DEPARTMENT OF MEDICINE, HUDDINGE, UNIT OF HEART AND LUNG DISEASES
Karolinska Institutet, Stockholm, Sweden

ATRIAL FIBRILLATION AND LIFESTYLE FACTORS WITH FOCUS ON PHYSICAL ACTIVITY AND ALCOHOL CONSUMPTION

Nikola Drča

Karolinska Institutet

Stockholm MMXVII

Published by Karolinska Institutet.
Printed by E-Print AB MMXVII

ISBN 978-91-7676-587-6

ATRIAL FIBRILLATION AND LIFESTYLE FACTORS WITH FOCUS ON PHYSICAL ACTIVITY AND ALCOHOL CONSUMPTION

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Nikola Drča

Principal Supervisor:
Professor Mats Jensen-Urstad
Karolinska Institutet
Department of Medicine, Huddinge
Unit of Heart and Lung disease

Co-supervisor(s):
Associate Professor Susanna C. Larsson
Karolinska Institutet
Institute of Environmental Medicine
Unit of Nutritional Epidemiology

Per Insulander
Karolinska Institutet
Department of Medicine, Huddinge
Unit of Heart and Lung disease

Hamid Bastani
Karolinska Institutet
Department of Medicine, Huddinge
Unit of Heart and Lung disease

Opponent:
Professor Hein Heidbuchel
University of Antwerp
Department of Cardiology

Examination Board:
Professor Mårten Rosenqvist
Karolinska Institutet
Department of Clinical Sciences, Danderyd Hospital

Professor Karin Schenck-Gustafsson
Karolinska Institutet
Department of Medicine, Solna
Centre for Gender Medicine

Associate Professor Håkan Walfridsson
Linköping University
Department of Medical and Health Sciences
Division of Cardiovascular Medicine

"But every road is tough to me. That has no friend to cheer it."

Elizabeth Shane

To Miriam, Baltasar and Sakarias.

ABSTRACT

The overall aim of this thesis was to investigate how modifiable lifestyle factors, with a focus on alcohol consumption and physical activity, influence the risk of atrial fibrillation (AF). The thesis is based on data from two prospective cohort studies of Swedish men (Cohort of Swedish Men) and women (Swedish Mammography Cohort). During 1997, 48,850 men who were born between 1918 and 1952 and lived in Västmanland and Örebro counties and 39,227 women who were born between 1914 and 1948 and lived in Västmanland and Uppsala counties completed a questionnaire about lifestyle and other risk factors for chronic diseases. Information was also gathered from Swedish Inpatient Register, Cancer Registry, Death Registry, and Diabetes Register.

In **paper I**, we examined the association between alcohol consumption and AF risk in a prospective study of Swedish men and women (n= 79,019) and conducted a meta-analysis of prospective studies (n =7). Alcohol consumption was associated with increased risk of AF in the two Swedish cohorts and in the meta-analysis of all studies. Even moderate intake was associated with increased risk of AF.

In **paper II**, we investigated the association of physical activity, at different ages and of different types, with risk of AF in a large (n = 48,850) general male population. High level of leisure-time exercise (moderate-intensity to high-intensity physical activity) in younger men was associated with an increased risk of AF later in life. On the other hand, walking/bicycling (low- intensity to moderate-intensity) at an older age was associated with a reduced AF risk.

In **paper III,** we evaluated the association between physical activity, at different ages and of different types, with risk of developing AF in a large (n = 39,227) general female population. Regular physical activity was associated with a reduced risk of AF in women. Moderate amount of daily physical activity was sufficient to have a significant risk reduction in middle-aged and elderly women. High levels of leisure-time exercise (moderate-intensity to high-intensity physical activity) were not a risk factor for AF in women as previously described in men.

In **paper IV** we investigated the joint association of four modifiable lifestyle factors (alcohol consumption, body mass index, regular exercise and smoking) on incidence of AF in both men and women. The combination of adopting four healthy lifestyle factors was associated with a halving of the risk of AF.

In **conclusion** alcohol consumption was associated with an increased risk of AF. A high level of intense physical activity may increase the risk of AF in younger men while low-moderate intense physical activity seems to decrease the risk in both men and women. High levels of intense physical activity were not a risk factor for AF in women. Adopting a healthy lifestyle may significantly reduce the risk of AF in both men and women. AF may partly be preventable through modifiable lifestyle behaviors. Our findings underscore the importance of avoidance of an unhealthy lifestyle.

LIST OF ORGINAL PAPERS

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

I. Larsson SC, Drca N, Wolk A.

Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis.

J Am Coll Cardiol. 2014;64:281-9.

II. Drca N, Wolk A, Jensen-Urstad M, Larsson SC.

Atrial fibrillation is associated with different levels of physical activity levels at different ages in men.

Heart. 2014;100:1037-42.

III. Drca N, Wolk A, Jensen-Urstad M, Larsson SC.

Physical activity is associated with a reduced risk of atrial fibrillation in middle-aged and elderly women.

Heart. 2015;101:1627-30.

IV. Larsson SC, Drca N, Jensen-Urstad M, Wolk A.

Combined impact of healthy lifestyle factors on risk of atrial fibrillation: Prospective study in men and women.

Int J Cardiol. 2016;203:46-9.

CONTENTS

1 Introduction 6
1.1 Definition 6
1.2 Epidemiology 8
1.3 Symptoms and Prognosis 8
1.3.1 Stroke risk in atrial fibrillation 9
1.3.2 Mortality and morbidity 9
1.4 Risk factors and associated medical conditions 9
1.4.1 Alcohol 10
1.4.2 Physical activity 11
1.4.3 Other modifiable risk factors 13
1.5 Management and Treatment 14
1.5.1 Stroke prevention 14
1.5.2 Risk factor management and assessment of underlying cardiovascular condition 15
1.5.3 Rhythm control or rate control 15
2 Aims 17
3 Methods 18
3.1 Study population 18
3.1.1 Swedish Mammography Cohort 18
3.1.2 Cohort of Swedish Men 18
3.2 National Health registries 19
3.2.1 The Swedish National Patient Register 19
3.2.2 The Swedish Cancer Register 19
3.2.3 The Swedish Cause of Death Register 20
3.2.4 Swedish National Diabetes Register 20
3.3 Assesment of exposure 20
3.3.1 Alcohol (Paper I) 20
3.3.2 Physical activity (Paper II and III) 20
3.3.3 Other lifestyle factors; Smoking and BMI (Paper IV) 22
3.3.4 Comorbidities and other information 22
3.4 Assessment of outcome 23
3.5 Follow up-time 23
3.6 Statistical analysis 23
3.6.1 Statistical methods 23
3.6.2 Missing values 23
3.7 Meta-analysis 24
3.7.1 Selection of Studies 24
4 Results 25
4.1 Paper I: Alcohol consumption and the risk of atrial fibrillation 25
4.2 Paper II: Physical activity and the risk of atrial fibrillation in men 29
4.3 Paper III: Physical activity and the risk of atrial fibrillation in women 32

4.4 Paper IV: Lifestyle factors and the risk of atrial fibrillation 33
5 Discussion 36
5.1 Main findings and general discussion 36
5.2 Methodology 38
5.2.1 Information bias 38
5.2.2 Selection bias 39
5.2.3 Confounding 39
5.2.4 Publication bias 39
6 Conclusion 40
7 Future perspectives 41
8 Sammanfattning (Summary in Swedish) 43
9 Acknowledgments 44
10 References 46

LIST OF ABBREVIATIONS

AF	Atrial Fibrillation
BMI	Body Mass Index
CI	Confidence Interval
COSM	Cohort of Swedish Men
DM	Diabetes Mellitus
EACTS	European Association for Cardio-Thoracic Surgery
EHRA	European Heart Rhythm Association
ESC	European Society of Cardiology
ICD	International Classification of Disease
IHD	Ischemic Heart Disease
LAA	Left Atrial Appendage
NOAC	Novel Oral Anticoagulant
NPR	National Patient Register
OAC	Oral Anticoagulants
PIN	Personal Identification Number
RR	Relative Risk
SCR	Swedish Cancer Register
SMC	Swedish Mammography Cohort
TIA	Transient Ischemic Attack
WHO	World Health Organization

1 INTRODUCTION

In the last decade, there has been an explosion of research in the field of AF. In the PubMed database through December 2016 more than 29,000 articles had AF in their title and more than 5,000 were published during the last two years. The extensive progress of the past decade has been made in understanding the pathophysiology, in developing new treatment options and in reducing the risk of thromboembolic complications but despite all the progress there remains a considerable need for improvement in the management of AF.

The aim of the studies in this thesis was to focus on modifiable lifestyle factors that could influence the risk of AF and which could be used to improve the management of AF.

1.1 DEFINITION

According to the 2010 ESC Guidelines for the management of AF is defined as a cardiac arrhythmia with the following three characteristics [1]:

(1) The surface ECG shows 'absolutely' irregular RR intervals (AF is therefore sometimes known as arrhythmia absoluta), i.e. RR intervals that do not follow a repetitive pattern.

(2) There are no distinct P waves on the surface ECG. Some apparently regular atrial electrical activity may be seen in some ECG leads, most often in lead V1.

(3) The atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and <200 milliseconds (>300 beats per minute).

There is an agreement that at least a 30 second long episode of the above described arrhythmia is diagnostic for an episode of AF [2].

In the four studies included in this thesis the outcome of AF was defined as either a diagnosis of AF or of atrial flutter because of these two arrhythmias close interrelationship and the difficulties differentiating between these conditions [3, 4].

AF has traditionally been classified in 5 different categories based on their presentation, clinical duration and spontaneous termination; First diagnosed AF, paroxysmal AF, persistent AF, long-standing persistent AF and permanent AF [5]. See Table 1 adopted from 2016 ESC Guidelines for the management of AF developed in collaboration with EACTS. The natural course of AF is that it usually progresses from short attacks of paroxysmal AF to more sustained attacks of persistent AF and eventually to permanent AF. Only a minor portion (2-3 %) of AF patients will continue to stay in the paroxysmal group during the following several decades [1]. Treatment could also change the pattern of AF from persistent to paroxysmal and a patient could have attacks of both paroxysmal and persistent AF.

TABLE 1. CLASSIFICATION OF ATRIAL FIBRILLATION

AF CLASSIFICATION	Definition
FIRST DIAGNOSED AF	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
PAROXYSMAL AF	Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days. AF episodes that are cardioverted within 7 days should be considered paroxysmal.
PERSISTENT AF	AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more.
LONG-STANDING PERSISTENT AF	Continuous AF lasting for ≥1 year when it is decided to adopt a rhythm control strategy.
PERMANENT AF	AF that is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as 'long-standing definition, not pursued in patients with permanent persistent AF'.

Classification into these categories based on the duration of the AF episode has some clinical relevance since it has been shown that outcome of therapy such as catheter ablation is associated with the AF episode duration. There is better outcome in paroxysmal than in long-standing persistent AF following catheter ablation [6].

Unfortunately, this classification does not consider mechanistic factors and modifiable risk factors for AF which precludes the implementation of an individual treatment strategy for each patient. In recent years, there have been attempts to introduce a new classification based on major causes or mechanistic factors for AF. Examples of such factors are atrial fibrosis, fatty or inflammatory infiltration in the atrial tissue, ion-channel dysfunction and autonomic imbalance of the nervous system. A classification that takes into account mechanistic factors and major risk factors for AF will assist in the formulation of more individual treatment strategies and hopefully also population based prevention strategies [7, 8].

1.2 EPIDEMIOLOGY

AF is the most common arrhythmia of clinical significance. The prevalence of AF is estimated in recent studies to be around 3 % among adults age 20 years or older [9, 10]. The prevalence of AF rises with increasing age. It is uncommon in younger age with prevalence < 0.2 % in people < 35 years but becomes a common medical condition in older age with a prevalence over 14 % in those older than 80-85 years [9-11]. The incidence and prevalence of AF is higher in men than in women in all age intervals. The increase of AF prevalence in recent studies compared to older studies is probably attributed to better diagnostics, an aging population and that older studies mostly included patients with permanent AF.

1.3 SYMPTOMS AND PROGNOSIS

AF can give a wide variety of symptoms such as general fatigue, rapid and irregular heartbeat, dizziness, shortness of breath, anxiety, weakness, faintness or confusion, decreased exercise tolerance, sweating and chest pain. The symptom severity may vary from being totally asymptomatic to highly symptomatic affecting the person's everyday life. Asymptomatic episodes of AF are common even in patients who have symptoms of AF. Since 2007 there is a classification of symptoms based on the impact on the patient's daily activity during presumed episodes of AF. The classification is called the EHRA symptom scale and has been validated and widely used. In 2014 a modified version was proposed and also recommended by the ESC to be used for treatment decision and in research studies (Table 2) [5, 12].

Table 2. Modified EHRA symptom scale

Modified EHRA score	Symptoms	Description
1	None	AF does not cause any symptoms.
2a	Mild	Normal daily activity not affected by symptoms related to AF.
2b	Moderate	Normal daily activity not affected by symptoms related to AF, but patient troubled by symptoms.
3	Severe	Normal daily activity affected by symptoms related to AF.
4	Disabling	Normal daily activity discontinued.

An EHRA symptom score of 2b is at present regarded to be the appropriate treatment threshold for intervention such as catheter ablation.

1.3.1 Stroke risk in atrial fibrillation

AF is an independent risk factor for stroke. The risk is 4 to 5 times higher compared with persons without AF. In the presence of mitral stenosis the risk is further increased up to 20 times [13]. Patients with asymptomatic, paroxysmal, persistent and permanent AF all have an increased risk for stroke but it seems that patients with persistent and permanent AF have a slightly higher risk for thrombo-embolic event (stroke or systemic embolism) and all-cause mortality compared with patients with paroxysmal AF [14, 15]. The risk of stroke in patients with non-valvular AF varies among patients depending on several risk factors. Clinically applicable stroke risk schemes have been developed and are still being refined. Today European and US guidelines advocate the use of the CHA2DS2-VASc score for estimating stroke risk in AF patients and for guidance off oral anticoagulant treatment [5, 16]. Points are given for different risk factors. One point each for the presence of congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65–74 years and female gender, and two points for age ≥75 years and previous stroke or TIA. The stroke risk increases with higher points. Patients without any of the afore mentioned risk factors and a score of zero are not recommended anticoagulant treatment. In male patients with a score of 1 point and in female patients with 2 points oral anticoagulant treatment should be considered while it is a clear indication in a male patient with 2 points and a female patient with 3 points [5].

1.3.2 Mortality and morbidity

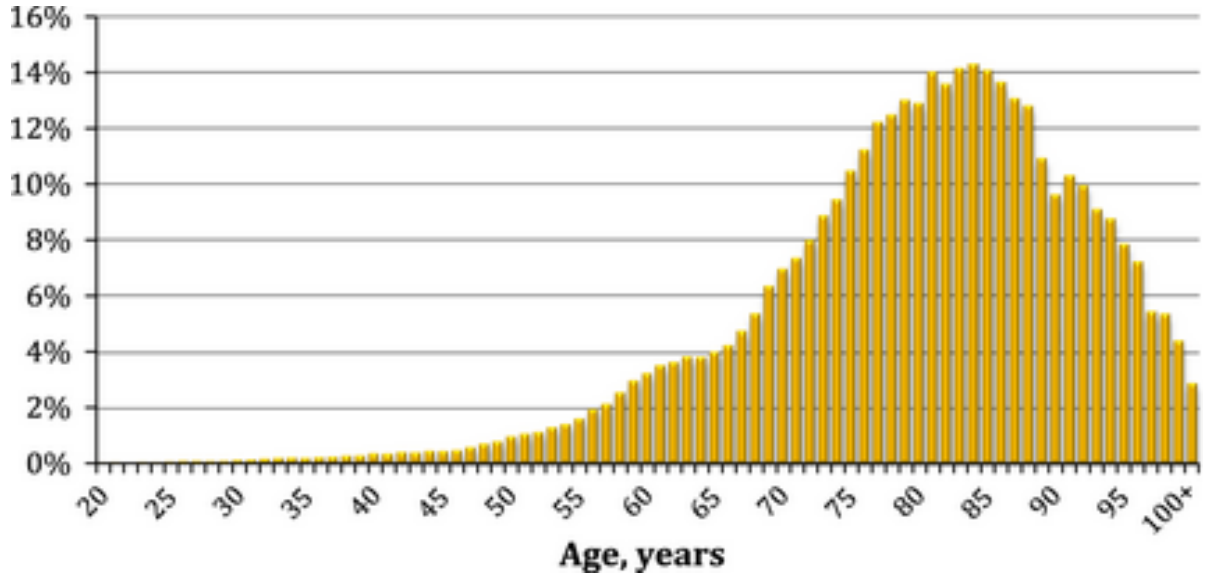
AF doubles the risk of all-cause mortality in women and increases the risk in men by about 50% [17, 18]. AF triples the risk for heart failure and doubles the risk for dementia [19-21]. The associations between dementia and AF could partially be explained by the increased risk of clinical stroke, but other mechanisms, including silent cerebral infarcts, microbleeds, and cerebral hypoperfusion, could be additional contributors [22]. Despite evidence based therapy there is still a considerably high morbidity and mortality.

1.4 RISK FACTORS AND ASSOCIATED MEDICAL CONDITIONS

The vast majority of published scientific papers during the last decades have been orientated in treatment of AF and prevention of stroke. Comparably little attention has been focused on prevention of AF. Several risk factors and associated medical condition linked to AF have been identified.

Age is a major predictor of AF. Both incidence rate and prevalence rise with increasing age in both men and women [10] (Figure 1).

Figure 1. Prevalence of diagnosed AF in relation to age on 31 December 2010 in Sweden



Male sex is an independent risk factor for AF and is associated with a 1.5-fold higher risk compared to women. Women with AF having similar stroke risk factors as men have however greater risk of having a stroke and maybe even a higher risk of death [18]. Adult height has also been observed to be strongly positively associated with AF in observational studies [23, 24]. None of the above mentioned risk factors are modifiable. Obesity and hypertension are the two modifiable factors that carry the largest population-attributable risks [25]. There are several others risk factors and medical conditions associated with AF; heart failure, valvular heart disease, myocardial infarction, chronic obstructive pulmonary disease, obstructive sleep apnea, chronic kidney disease, thyroid dysfunction, smoking and genetic predisposition.

It is important to identify modifiable risk factor to decrease the burden of AF and devise improved management strategies. AF prevalence is increasing worldwide due to an ageing population and increasing prevalence of causative risk factors of AF. The health cost driven by complications of AF, such as stroke, and treatment cost will rise dramatically unless better prevention strategies are developed. In this thesis, we will focus on the modifiable risk factors alcohol consumption and physical activity and their association with AF.

1.4.1 Alcohol

Alcohol is a toxic substance that has deleterious effects on health. Liver cirrhosis is probably the best known but it can cause a wide variety of conditions such as dementia, breast cancer,

colorectal cancer, upper digestive tract cancer, injuries and accidents, and alcohol dependency [26]. Dilated cardiomyopathy is associated with heavy consumption over an extended period [27]. Alcohol consumption is one of the top contributors to the global burden of death and disability. It is estimated that alcohol attributes to the global burden of death with 3.8 % and with 4.6% to the global disability-adjusted life-years [28]. Despite that, the general media and the public have in the last decades focused on the positive effects of alcohol and in particular on positive effects on IHD. There are indications from epidemiologic studies that low to moderate alcohol consumption (<30g/day) may decreases the risk of IHD and ischemic stroke. Women appears to have a larger positive effect with low consumption but it transforms to a harmful effect at a lower level of average alcohol consumption compared to men [29]. Drinking pattern is important and episodic heavy drinking has not shown to be protective for IHD [30].

Already in the early 70´s an association between acute alcohol consumption and cardiac arrhythmia was observed. The term "Holiday heart syndrome" was coined by Philip Ettinger 1978 when he described an association between cardiac arrhythmia most frequently AF after binge drinking in otherwise healthy people. The name "Holiday heart syndrome" comes from the observation that the arrhythmia episodes were observed after weekends or public holidays [31].

A standard drink is equivalent to 12 g of alcohol. This amount corresponds approximately to 4 cl liquor, 8 cl strong wine, 15 cl wine, 33 cl class III beer (alcohol by volume, >3.5%), 50 cl class II beer (2.8−3.5%), or 66 cl class I beer (<2.25%). Binge drinking is the consumption of ≥5 drinks per occasion. High alcohol consumption is the consumption of >60g per day in men and >40 g per day in women, moderate alcohol consumption is 20–60g per day in men and 10–40g per day in women and light drinking relates to <20g per day in men and <10g per day in women [32].

Consuming moderate to high amounts of alcohol on a regular basis may increase the risk of developing AF [33-37]. However, the association between light and moderate drinking and incident AF is less well studied.

1.4.2 Physical activity

The definition of physical activity is any bodily movement produced by skeletal muscles that result in energy expenditure. Exercise is defined as a subcategory of physical activity that is planned, structured and has a purpose of improving or maintaining physical fitness [38].

The gold standard for measurements of free-living total energy expenditure is the doubly-labeled water method [39]. Doubly labeled water is an excellent method to measure total energy expenditure in humans over a period of 1–4 weeks. The limitation is that it is expensive, unsuitable for large population studies and does not provide information of type and intensity. There are several other techniques to measure or estimate physical activity. There is behavioral observation, questionnaires (including diaries, recall questionnaires and

interviews) and physiological markers like heart rate monitoring and different kinds of sensors for motion.

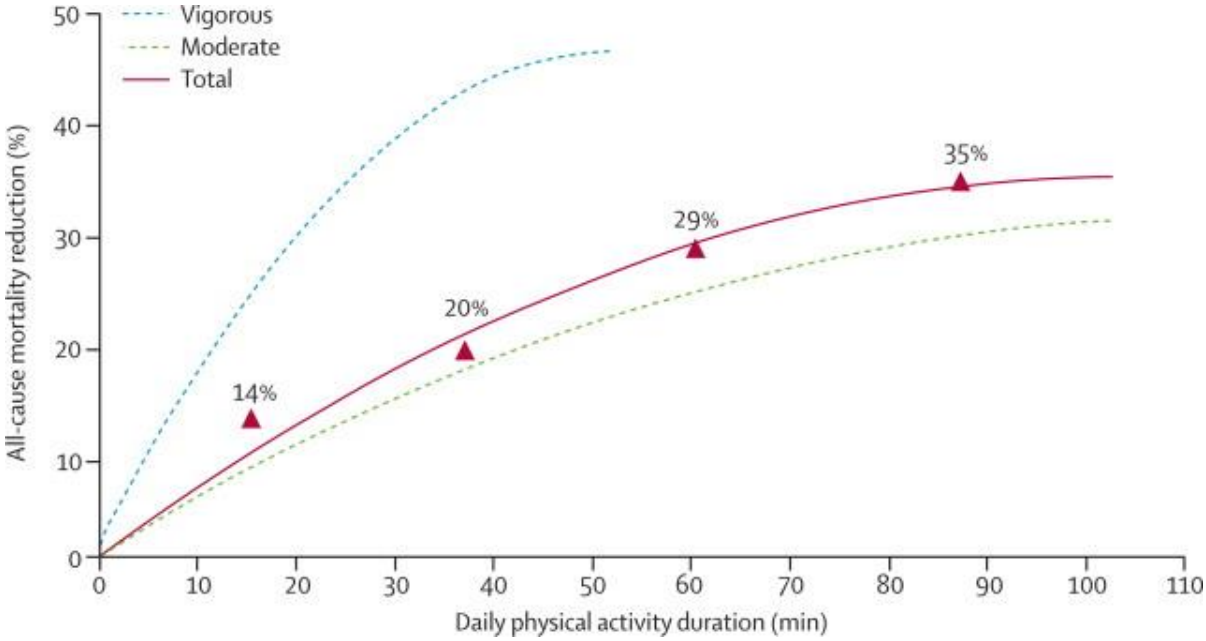
When it comes to measure physical activity in a large population sample over a long period there is no golden standard. Self-reported physical activity questionnaires are the most common method for assessment of physical activity in large epidemiological studies. It is cheap, and relatively easy to administrate to a large study population. The drawback is lower reliability and validity and it is probably best used as an activity-ranking instrument [40].

Physical activity is a modifiable health related factor that contributes to the prevention and management of different medical conditions and diseases. Regular physical activity is associated with a lower risk for important medical conditions such as cardiovascular disease, cerebrovascular disease, hypertension, obesity, DM, osteoporosis, some malignancies, and mental illness [41-45].

The American College of Sports Medicine and the Centers for Disease Control and Prevention published 1995 national guidelines for physical activity. A minimum of 30 min of moderate-intensity physical activity was recommended most days a week. An updated recommendation came in 2007 which clarified the recommended frequency for moderate-intensity and furthermore, recommendation for vigorous intensity physical activity was incorporated. The 2007 recommendation for an adult is a minimum of moderate-intensity physical activity for 30 min on five days per week or vigorous-intensity aerobic physical activity for a minimum of 20 min on three days per week. Combinations of moderate- and vigorous-intensity activity can be performed to meet this recommendation [46]. There is a dose-response relation between physical activity and health and for the majority of health outcomes better outcomes will occur with higher intensity, longer duration and greater frequency [47] (Figure 2).

However, some studies raised the doubt that exercise may be associated with higher incidence of AF. Several small case-control studies reported that long-term regular sport activity was associated with higher risk of AF in young and middle-aged men[24, 48-51]. On the other hand, a prospective study of older men and women observed a reduction in risk of AF with moderate-intensity physical activity and no increase in risk with more intense physical activity[52]. It seems that there was a more complex association between physical activity and AF and that the association could be J or U-shaped. Furthermore, studies in women were scarce and very few studies included women.

Figure 2. Daily physical activity duration and all-cause mortality reduction in a cohort of 416,175 individuals aged 20 years with an average follow-up of 8.05 years.



Reprinted from The Lancet, reference [47] with permission from Elsevier.

1.4.3 Other modifiable risk factors

Obesity (BMI ≥30 kg/m^2) is a growing problem worldwide. According to the WHO, the worldwide prevalence of obesity has doubled since 1980. In 2014 it was estimated that about 13% of the world's adult population were obese and 39 % overweight (BMI≥25 kg/m^2). Several cohort and case-control studies have shown that obesity and overweight are associated with an increased risk of AF [53]. The Framingham Heart Study observed a 4% increase in risk of AF per 1-unit increase in BMI for both men and women in a multivariable-adjusted model [54]. A recent meta-analysis also highlighted that obesity is a risk factor for having AF after surgery or relapsing in AF after catheter based ablation of AF [53]. The Women´s Health Study demonstrated that women who lost weight during the study period decreased their risk of AF while the opposite happened to women who gained weight [55]. This concept of decreasing AF burden and symptom severity with weight reduction was also observed in the prospective LEGACY study [56]. They observed that sustained weight loss, particularly with avoidance of weight fluctuation, was associated with a dose-dependent reduction in AF burden and maintenance of sinus rhythm.

Hypertension is a risk factor both for AF and stroke and a good blood pressure control is crucial [57]. Antihypertensive drugs reduce the risk for AF mainly by lowering blood pressure [58]. It has been suggested that specific antihypertensive medication could have additional effects. Some studies have suggested that blockade of the renin–angiotensin system with angiotensin-converting enzyme inhibitors or an angiotensin receptor blockers

could decrease the risk of AF through atrial remodeling [59]. There are studies showing that beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers could reduce the risk for AF compared with calcium-channel blockers in patients with hypertension [60, 61].

Smoking is an established cardiovascular risk factor and the leading preventable cause of premature disease and death [62]. Several studies have shown smoking to be a risk factor for AF while others have been unable to show any association [20, 63-66]. A recent meta-analysis of 16 prospective cohort studies showed that smoking is associated with a modest increased risk of incident AF [67]. There are no randomized trials proving that smoking cessation reduces the risk of AF. Health care professionals should encourage individuals to quit smoking to reduce disease and prevent premature death.

DM is an independent risk factor for AF and the risk for AF increase with longer duration and worse glycemic control [57, 68]. In the ARREST-AF trial a strategy of aggressive risk factor modification on multiple risk factors including weight loss and improved glycemic control reduced the risk of recurrent AF after catheter ablation [69]. In the ACCORD trial an intensive glycemic control targeting a glycated hemoglobin level of <6.0% compared to standard strategy targeting a glycated hemoglobin of 7.0-7.9% was not able to reduce the risk for new onset AF in DM patients [70].

Obstructive sleep apnea, has been associated with an increased risk of AF [71, 72]. Treatment of sleep apnea with continuous positive airway pressure reduces the risk of relapsing in AF in patients undergoing catheter ablation with pulmonary vein isolation, after electrical cardioversion and in patients who were managed medically [73, 74]. Obesity and being overweight is associated with sleep apnea and weight reduction reduces the severity of sleep apnea and AF [56, 75].

1.5 MANAGEMENT AND TREATMENT

Generally, there are three aspects in the management of atrial fibrillation.

1) Stroke prevention
2) Manage risk factors and underlying cardiovascular conditions
3) Reset the rhythm or control the rate

1.5.1 Stroke prevention

Stroke prevention is the most important therapeutic goal in management of AF. OAC is recommended for stroke prevention and CHA2DS2-VASc score for estimating stroke risk in non-valvular AF. There are two types of OAC; warfarin (vitamin K antagonist) and NOACs (non-vitamin K antagonists). In a meta-analysis of 29 trials warfarin reduced the risk of stroke by 64% compared to controls (aspirin or no treatment)[76]. Since 2011 NOACs have been introduced as alternatives to warfarin for prevention of stroke in patients with non-valvular AF and in the most recent guidelines from ESC NOACs are recommended in

preference to warfain when OACs are initiated in patients with AF who are eligible for NOACs. In patients with mechanical heart valves or moderate to severe mitral stenosis, warfarin is recommended and NOACs are not recommended [5].

LAA is the primary source for embolus in AF specially in non-valvular AF and 90 % of emboli are considered to originate from LAA [77]. Exclusion or occlusion of the LAA has been used to reduce the stroke risk in AF patients. Both surgical and percutaneous device strategies are available for occlusion or exclusion. Currently only one device (Watchman®) has been compared with warfarin in randomized controlled trials. The Watchman®, a percutaneous closure device of the LAA, showed non-inferiority to warfarin treatment for prevention of stroke in AF patients with moderate risk of stroke. The Watchman® device is mainly used in patients with contraindication for OAC [78]. Surgical occlusion or exclusion in patients undergoing cardiac surgery has been done for many years but large randomized trials are not available to determine the effect in stroke prevention compared to OAC.

1.5.2 Risk factor management and assessment of underlying cardiovascular condition

When treating a patient with AF it is important to identify risk factors and underlying cardiovascular conditions to optimize treatment. Risk factors including obesity, hypertension, diabetes, obstructive sleep apnea, excessive alcohol consumption, smoking, sedentary lifestyle, that have been mentioned and discussed in previous chapters should be addressed. Underlying cardiovascular conditions including valvular heart disease, heart failure and elevated blood lipids should be diagnosed and treated. In the ARREST-AF cohort study aggressive risk factor management with a combination of blood pressure control, weight management with diet and exercise, lipid management, glycemic control, management of obstructive sleep apnea and support for smoking cessation and reduction in alcohol intake markedly improved the long-term success after AF ablation [69].

1.5.3 Rhythm control or rate control

The two treatment strategies to manage AF are rate control or rhythm control. Rhythm control is aimed at restoration and maintenance of sinus rhythm while rate control accepts the AF and the aim is to regulate the rate. The optimal heart rate in rate controlled AF patients is currently unclear. A ventricular rate of <80 beats per minute at rest and <115 beats per minute at moderate exercise is often recommended [79]. In the RACE II trial which was a randomized controlled trial with the intention to investigate if lenient rate control (resting heart rate <110 beats per minute) is not inferior to strict rate control (resting heart rate <80 beats per minute) for preventing cardiovascular morbidity and mortality in patients with permanent AF it was noted that lenient rate control was non-inferior to more strict rate control. However, the actual rate difference between the two groups at the end of the first year of the study was not so large (86±15 in lenient group and 75±12 in strict group). In the European guidelines a lenient rate control is recommended as an initial approach, unless patient is highly symptomatic and requires a stricter rate control [5]. In the US guidelines a

more strict rate control (<80 beats per minute) is considered reasonable and a lenient rate control just in patient who remain asymptomatic and have a preserved left ventricular function [80]. Rate control could also be accomplished by AV-nodal ablation and permanent ventricular pacing. This approach is only recommended in patients after rate control with medication has been attempted and rhythm control is not possible. Rhythm control could be achieved either with the help of antiarrhythmic drugs, electrical cardioversion, catheter ablation, surgical procedures (both surgical ablation and cut-and-sew technique) or a combination of these methods. Catheter ablation is a minimally invasive rhythm control procedure and surgical procedures are mainly done in patients undergoing cardiac surgery for indications other than AF [81]. Studies comparing rhythm control with antiarrythmic drugs versus rate control have not been able to show any survival benefit with rhythm control [82-84]. Catheter ablation performed at experienced centers is more effective than antiarrythmic drugs in maintaining sinus rhythm and improves the quality of live [85-87]. It is still unclear if catheter ablation improves the long-time survival and reduces cardiovascular events but this is under investigation. Currently rhythm control is indicated for symptom improvement in AF patients.

2 AIMS OF THE THESIS

The overall aim of this thesis was to investigate whether modifiable life style factors influence the risk of atrial fibrillation in a general population.

The specific aims of the studies were to investigate:

1. Whether alcohol consumption influences the risk of atrial fibrillation among men and women.

2. The association between physical activity and risk of atrial fibrillation in a general population of men.

3. The association between physical activity and risk of atrial fibrillation in a general population of women.

4. The overall inpact of a combination of healthy lifestyle factors on the risk of atrial fibrillation.

3 METHODS

3.1 STUDY POPULATION

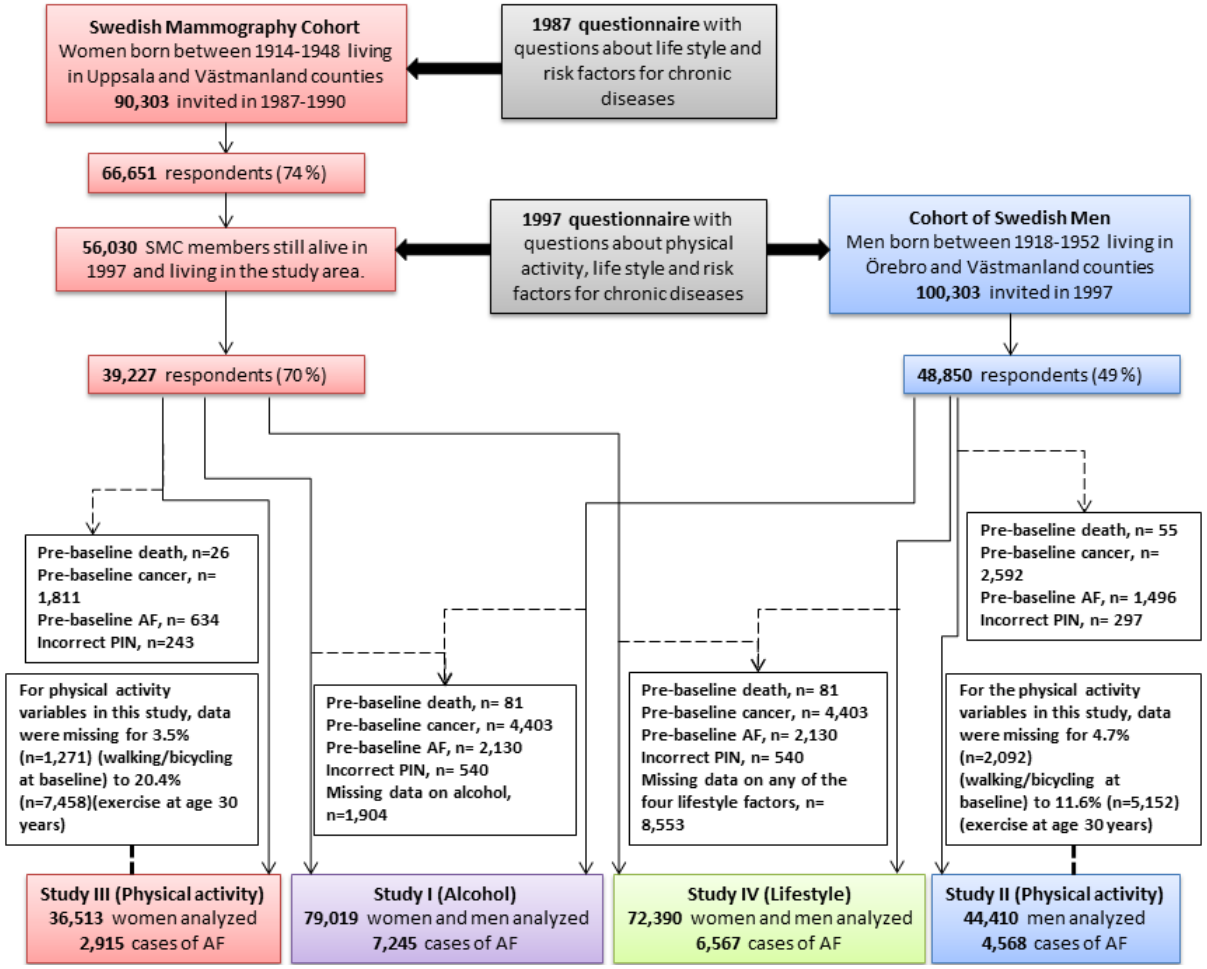
3.1.1 Swedish Mammography Cohort

SMC is a population based cohort established between 1987 and 1990 when all women (n = 90,303) who lived in Uppsala and Västmanland counties and were born between 1914 and 1948 received an invitation for a mammography screening program together with a diet and lifestyle questionnaire. In 1997 a second extended questionnaire was sent out to all women in the original cohort who were still alive (n = 56,030). The questionnaire in 1997 included questions about physical activity, alcohol consumption, history of cigarette smoking, body weight across the life course, height and other questions about lifestyle and risk factors for chronic diseases. The response rate for the 1997 questionnaire was 70 % (n = 39,227). Information from the 1997 questionnaire was used for the exposure assessment in all studies in this thesis that included women (Study I, III and IV).

3.1.2 Cohort of Swedish Men

The population based COSM was established 1997 when all men (n=100,303) born between 1918 and 1952 living in Västmanland and Örebro counties received an invitation to participate in the study along with a self-administered questionnaire. It was the same questionnaire used for the women in the SMC in 1997 except for some sex specific questions. Of the eligible men, 48,850 (49%) completed the questionnaire. Information from the 1997 questionnaire was used for the exposure assessment in all studies in this thesis that included men (Study I, II and IV).

Figure 3. Source population, exclusions and study population for study I-IV



3.2 NATIONAL HEALTH REGISTRIES

3.2.1 The Swedish National Patient Register

The Swedish NPR also called Hospital Discharge Register that started as a trial in 1964 has since 1987 full national coverage of all in-hospital specialist care of somatic and psychiatric care. The NPR contains information about both primary and secondary diagnosis coded according to the Swedish ICD system (adapted from WHO ICD classification system). Since 2001 it also contains information from out-hospital specialist care. Since the start of the NPR, primary diagnoses are missing in only 0.8% of somatic care [88].

3.2.2 The Swedish Cancer Register

The SCR was founded in 1958 and covers the whole population. All health care providers are obliged to report newly detected cancer cases to the registry. The most recent quality study for the SCR was published in 2009 and it was a sample survey from 1998 and it estimated the underreporting to be less than 4% [89].

3.2.3 The Swedish Cause of Death Register

Sweden has one of the oldest population statistics in the world. Already in 1749 a nationwide reporting system was developed. The priest in the parish was required to report causes of death in the population. The current Causes of Death Register contains information from 1961. 93 % of all deaths are reported within 10 days and 100 % within 30 days. The cause of death in missing in 1-2 % [90].

3.2.4 Swedish National Diabetes Register

The National Diabetes Register was initiated in 1996 as a registry to assure quality and support diabetic care. Trained nurses and physicians collect data during regular appointments at specialist clinics and primary healthcare centers nationwide and report at least once a year either online or by electronic transmission of patients' charts. During the past 20 years, the coverage has grown and in 2015 the register covered 90 % of all adults with type II diabetes and its use in medical research has grown [91]. The coverage in 2009 was estimated to be 70 %.

3.3 ASSESSMENT OF EXPOSURE

3.3.1 Alcohol (Paper I)

Alcohol consumption was assessed in the self-administered questionnaire where participants reported their alcohol consumption status (never, former and current drinker of alcohol) and their average consumption of 96 foods and beverages, including 6 alcoholic beverages, during the past year. They reported how often they consumed class I beer (<2.25%, alcohol by volume), class II beer (2.8% to 3.5%), class III beer (>3.5%), wine, strong wine, and liquor as well as the amount they usually drank at each occasion. The amount of alcohol consumption at each occasion was asked in an open-ended question and for the frequency of consumption there were 9 pre-defined categories, ranging from never to ≥3 times per day.

The questionnaire has been validated in a group of 248 men, and the Spearman correlation coefficients between estimates from the questionnaire, and the mean of 14 24-h recall interviews which were made during a period of one year was 0.81 for alcohol (ethanol) [92].

3.3.2 Physical activity (Paper II and III)

Physical activity was assessed by a self-administered questionnaire. The participants reported their physical activity level at work (mostly sitting down; sitting down about half of the time; mostly standing up; mostly walking, lifts, carry little; mostly walking, lifts, carry much; heavy manual labor), walking/bicycling (almost never, <20 min per day, 20–40 min per day, 40–60 min per day, 1–1.5 h per day, or >1.5 h per day), doing home/household work (<1, 1–2, 3–4, 5–6, 7–8, or >8 h per day) and leisure-time exercise (<1, 1, 2–3, 4–5, or >5 h per week). The questionnaire also included questions about inactivity; watching TV/reading (<1, 1–2, 3–4, 5–6, or >6 h per day) and an open question about hours per day sleeping or resting. In paper II and III we used information from physical activity levels on walking/bicycling

and leisure-time exercise. The participants were asked to assess their level of physical activity at current age (1997) and retrospectively at age 15, 30 and 50 years (Figure 4).

Figure 4. Physical activity question on walking/bicycling and leisure-time exercise in the 1997 questionnaire

Mark your level of physical activity at **different ages**

Walking/cycling	15 yrs	30 yrs	50 yrs	this yr
Hardly ever	☐	☐	☐	☐
Less than 20 min/day	☐	☐	☐	☐
20-40 minutes/day	☐	☐	☐	☐
40-60 minutes/day	☐	☐	☐	☐
1-1,5 hours/day	☐	☐	☐	☐
More than 1,5 hours/day	☐	☐	☐	☐

Leisure time

Exercise	15 yrs	30 yrs	50 yrs	this yr
Less than 1 hour/week	☐	☐	☐	☐
1 hours/week	☐	☐	☐	☐
2-3 hours/week	☐	☐	☐	☐
4-5 hours/week	☐	☐	☐	☐
More than 5 hours/week	☐	☐	☐	☐

The validity of the assessment of physical activity through the questionnaire used in the COSM was tested in 111 men, aged 44–78 years, by comparison with two 7-day activity records performed 6 months apart [93]. The Spearman correlation coefficients (adjusted for within-person and between-person variations in the records) between the questionnaire and activity records were 0.4 for combined walking/bicycling and exercise. It was also validated for women in the SMC using two 7-day activity records that were performed 12 months apart in 116 women (aged 56–75 years) randomly selected from the cohort [94]. Validity of combined exercise and walking/bicycling was 0.42; this was measured by deattenuated concordance correlations comparing the records with the questionnaire

3.3.3 Other lifestyle factors; Smoking and BMI (Paper IV)

Smoking

Smoking status was reported at baseline in the 1997 questionnaire. Participants reported their smoking status (never, past or current smoker) and smoking history throughout life. They were asked to report number of cigarettes per day at 15-20 years of age and then for every decade thereafter up to 60 years and at baseline in 1997. One pack-year was defined as 20 cigarettes per day for one year. There is no specific validation study on smoking status for the COSM or the SMC. Most studies have shown underreporting specially in groups where smoking is particularly undesirable such as pregnant women or individuals with smoking related disease [95].

BMI

Current weight in kilograms and height in centimeters at age 20 was reported at baseline in the 1997 questionnaire. Participants were asked to report their weight at 20 years of age and then for every decade thereafter up to 80 years. BMI was calculated using height at 20 years and weight at baseline in 1997. BMI was calculated by dividing weight (kg) with height squared (m^2). Swedish men and women tend to overestimate their height and underestimate their weight [96]. High validity has been observed for self-reported height ($r = 0.9$) and weight ($r = 0.9$) compared with actual measurement [96].

Definition of healthy lifestyle in paper IV

We analyzed four pre-specified modifiable lifestyle factors. BMI, regular exercise, alcohol consumption, and smoking. A healthy lifestyle score was created by dichotomizing each lifestyle factor into a predefined healthy lifestyle alternative and a less healthy behavior: BMI (<25 kg/m2 versus ≥25 kg/m2 [overweight]); regular exercise during the last year defined as walking or bicycling at least 20 min/day versus <20 min/day; alcohol consumption (no or light-to-moderate alcohol consumption [≤2 drinks/day for men and ≤1 drink/day for women] versus high consumption); and smoking (not smoking [never and past] versus current smoking). The allocated points of lifestyle factors were combined to create a healthy lifestyle score that ranged from 0 (no adherence to the healthy lifestyle) to 4 (full adherence).

3.3.4 Comorbidities and other information

Information about family history of myocardial infarction, history of hypertension, history of diabetes mellitus, history of coronary heart disease, education, and aspirin use was collected from the 1997 questionnaire. Information on coronary heart disease and heart failure was obtained from the Swedish NPR. Participants were classified as having diabetes if they self-reported diabetes on the questionnaire or had a diagnosis of diabetes recorded in Swedish NPR or the Swedish NDR.

3.4 ASSESSMENT OF OUTCOME

The outcome of AF was defined as either a diagnosis of AF or of atrial flutter because of their close interrelationship and the difficulties differentiating between these conditions. AF cases were identified by computerized linkage of the study cohort to the Swedish NPR using the Swedish Personal Identification Number. We used the codes 427.92 from ICD-8, 427D from ICD-9, and I48 (I48.0, I48.1, I48.2, I48.3, I48.4, I48.9) from ICD-10 to identify the diagnosis of AF and atrial flutter.

3.5 FOLLOW UP-TIME

Participants were followed up from January 1, 1998 until the date of diagnosis of AF, death (ascertained through linkage to the Swedish Death Register) or end of follow-up (December 31, 2009), whichever occurred first. The median follow-up was 12 years (10^{th} percentile 7.5 years, 90th percentile 12.0 years).

3.6 STATISTICAL ANALYSIS

3.6.1 Statistical methods

All the studies used Cox regression hazard models to estimate hazard ratios (referred to hereafter as relative risks [RR]) between exposure groups [97]. The time-scale used was the time-on-study time scale, defined as the time interval between the date of study entry and the date of study exit. Cox regression has the assumption that the ratio of the rates is constant during follow-up. We tested the proportional hazards assumption using the Schoenfeld residuals. We used the likelihood ratio test, comparing models with and without interaction terms, to assess statistical interaction. In **paper I**, the chi-square test we used for differences in associations for beverage types.

All analyses were performed using the statistical software SAS (V.9.3; SAS Institute, Cary, North Carolina, USA) except for the meta-analysis in **paper I** where we used Stata (version 12.0, StataCorp, College Station, Texas). All statistical tests were two-sided, and p values <0.05 were considered statistically significant.

3.6.2 Missing values

In all papers men and women with an erroneous or a missing PIN, those with a prior diagnosis of AF or cancer except non-melanoma skin cancer, and those who died between the administration of the questionnaire and start of follow-up were excluded.

In **paper I** participants with missing data on alcohol consumption were excluded.

In **paper II** and **III** if information about physical activity at baseline were missing, we used information for physical activity at age 50 years. Participants with missing data on leisure-time exercise or walking/bicycling were excluded from the corresponding analysis.

In **paper IV** we excluded men and women with missing data on any of the four lifestyle factors (BMI, walking/bicycling, alcohol consumption and smoking).

For detailed information see Figure 3.

3.7 META-ANALYSIS (PAPER I)

We performed a dose-response meta-analysis that included findings from the two Swedish prospective cohorts (COSM and SMC) and results from previously published; prospective studies to summarize the available data on the association between alcohol consumption and AF in **paper I**.

3.7.1 Selection of Studies

The PubMed database was used to identify relevant studies by a computerized search through January 10, 2014. We used the search terms alcohol consumption, alcohol drinking, or alcohol intake combined with AF or atrial flutter. Furthermore, we reviewed the reference lists of retrieved articles for further studies. No language restrictions were applied.

Eligibility criteria for inclusion in the meta-analysis were: 1) prospective design; 2) the exposure was alcohol consumption; 3) the outcome was incidence of AF or AF and atrial flutter combined; and 4) RRs with 95% CIs were reported for at least 3 categories of alcohol consumption to be able to estimate a dose-response trend. When there were duplicate publications from the same source population, we included the study with the largest number of AF cases. We did not include studies of recurrence of AF.

4 RESULTS

4.1 PAPER I: ALCOHOL CONSUMTION AND THE RISK OF AF

Prospective cohort study of COSM and SMC.

During a median follow-up of 12 years of 79,019 participants, including 43,841 men and 35,178 women (859,420 person-years), we ascertained 7,245 incident AF cases (4,488 in men and 2,757 in women). Baseline characteristics of the study population for the lowest and highest categories of alcohol consumption are shown in Table 3.

The associations of alcohol drinking status and consumption of total alcohol and different alcoholic beverages with risk of AF are presented in Table 4. The association between alcohol consumption and AF did not differ by sex (p for interaction = 0.74). All analyses were therefore conducted for men and women combined. Compared with current alcohol drinkers of <1 drink per week, consumption of 15−21 drinks per week and >21 drinks per week was associated with a statistically significant 14% and 39%, respectively, increased risk of AF.

Binge drinking (consumption of ≥5 drinks on a single occasion) was identified in 18% of current drinkers and was associated with an increased risk for AF after multivariable adjustment (age, sex, education, smoking, BMI, family history of MI, and histories of CHD, heart failure, diabetes, and hypertension) (RR: 1.13; 95% CI: 1.05-1.22). The association between binge drinking and AF was similar after further adjustment for frequency of consumption of each alcoholic beverage (RR: 1.12; 95% CI: 1.04-1.21) or for total alcohol consumption (drinks/week) (RR: 1.11; 95% CI: 1.03-1.20). Binge drinking of liquor (RR: 1.10; 95% CI: 1.02-1.19) and wine (RR: 1.24; 95% CI: 1.08-1.43), but not beer (RR: 1.02; 95% CI: 0.79-1.30), was associated with increased AF risk in a multivariable model adjusted for the other AF risk factors, mutually for liquor, wine, and beer, and for frequency of consumption of each alcoholic beverage. After excluding the binge drinkers, the association between total alcohol consumption and AF risk was slightly attenuated but still present; multivariable RRs (95% CI) were 1.11 (95% CI: 0.98 to 1.26) for 15 to 21 drinks/week and 1.34 (95% CI: 1.17 to 1.53) for >21 drinks/week compared with current drinkers of <1 drink/week.

Table 3. Baseline characteristics* of 79,019 Swedish men and women by alcohol drinking status and number of drinks per week

Characteristics	Alcohol drinking status						
	Never (n=6,428)	Past (n=3,743)	Current (drinks/wk†)				
			<1 (n=12,382)	1-6 (n=34,553)	7-14 (n=14,246)	15-21 (n=4,411)	>21 (n=3,256)
Age in years (mean)	67.0	64.1	63.3	60.1	58.0	57.1	56.9
BMI in kg/m^2 (mean)	25.8	26.0	25.6	25.2	25.4	25.8	26.1
Postsecondary education (%)	13.5	11.8	14.9	18.6	21.1	21.2	19.5
Current smokers (%)	8.9	34.3	21.5	24.1	27.1	30.1	38.2
Family history of MI (%)	15.6	18.5	17.5	16.1	15.3	16.3	16.5
History of diabetes (%)	8.1	15.1	7.5	6.5	6.7	6.8	9.3
History of hypertension (%)	21.6	27.8	22.7	21.5	22.6	23.8	27.2
History of coronary heart disease or heart failure (%)	5.1	11.5	5.6	6.2	6.7	8.1	7.1
Ever aspirin use (%)	38.8	43.2	43.8	43.2	41.6	40.1	40.1
Exercise ≥2 h/wk (%)	52.7	56.2	55.9	59.3	60.4	58.2	55.4
Walking/bicycling ≥40 min/d (%)	34.6	36.8	36.2	34.7	33.2	33.7	30.5

*All variables besides age are age-standardized. BMI , body mass index; MI, myocardial infarction.

†Consumption in standard drinks = 12 g alcohol/drink

Table 4. Relative risks (95% confidence intervals) of atrial fibrillation by alcohol drinking status and number of drinks of total alcohol, liquor, wine, and beer in current drinkers among 79,019 Swedish men and women

Alkohol drinking status	No. of Cases	Person-years	Age-adjusted RR (95% CI)	Multivariable RR (95% CI)*	Multivariable RR (95% CI)*†
Never	820	66,101	1.02 (0.93-1.12)	1.02 (0.93-1.12)	1.07 (0.93-1.12)
Past	406	36,765	1.02 (0.91-1.14)	0.96 (0.85-1.08)	1.01 (0.89-1.16)
Current, drinks/wk‡					
<1 (0.4)§	1,232	132,869	1.00 (reference)	1.00 (reference)	1.00 (reference)
1-6 (4.6)	2,909	381,029	0.99 (0.92-1.06)	1.01 (0.92-1.06)	1.06 (0.98-1.15)
7-14 (10)	1,162	158,611	1.05 (0.96-1.14)	1.07 (0.98-1.17)	1.12 (1.01-1.23)
15-21 (16.6)	381	4, 969	1.15 (1.02-1.30)	1.14 (1.01-1.28)	1.18 (1.03-1.35)
>21 (28.4)	335	35,076	1.42 (1.25-1.62)	1.39 (1.22-1.58)	1.43 (1.25-1.65)
P for trend¶			<.0001	<.0001	<.0001
Liquor, drinks/wk					
<1 (0.1)	3,993	629,590	1.00 (reference)	1.00 (reference)	1.00 (reference)
1-6 (2.3)	1,603	188,686	1.08 (1.02-1.15)	1.04 (0.97-1.11)	1.05 (0.97-1.12)
7-14 (8.8)	314	32,352	1.25 (1.11-1.41)	1.13 (1.01-1.28)	1.14 (1.00-1.30)
>14 (18.8)	109	8,792	1.69 (1.39-2.05)	1.43 (1.14-1.74)	1.46 (1.18-1.81)
P for trend¶			<.0001	0.0002	0.0002
Wine, drinks/wk					
<1 (0.2)	3,465	484,708	1.00 (reference)	1.00 (reference)	1.00 (reference)
1-6 (2.6)	2,128	319,913	0.99 (0.93-1.04)	1.02 (0.96-1.07)	1.02 (0.96-1.09)
7-14 (8.6)	331	45,248	1.11 (0.99-1.24)	1.09 (0.97-1.23)	1.07 (0.94-1.21)
>14 (18.6)	95	9,551	1.37 (1.11-1.68)	1.30 (1.06-1.61)	1.35 (1.08-1.68)
P for trend			0.003	0.009	0.01
Beer, drinks/wk					
<1 (0.1)	2,954	443,987	1.00 (reference)	1.00 (reference)	1.00 (reference)
1-6 (2.7)	2,196	303,557	0.95 (0.90-1.01)	0.96 (0.91-1.02)	1.00 (0.93-1.06)
7-14 (11.5)	584	72,041	1.09 (0.99-1.20)	1.07 (0.98-1.12)	1.11 (1.00-1.23)
>14 (21.2)	285	39,835	1.12 (0.98-1.27)	1.06 (0.93-1.23)	1.03 (0.87-1.19)
P for trend¶			0.02	0.14	0.28

*Multivariable models were stratified by age (in months) and sex and adjusted for education (primary school, high school, university), smoking status and pack years of smoking (never smoker, past smoker and <20 pack-years, past smoker and ≥20 pack-years, current smoker and <20 pack-years, current smoker and ≥20 pack-years), body mass index (<23.0, 23.0-24.9, 25.0-29.9, ≥30 kg/m^2), family history of myocardial infarction before 60 years of age (yes/no), history of coronary heart disease or heart failure (yes/no), history of diabetes (yes/no), history of hypertension (yes/no), aspirin use (yes/no), exercise (5 categories), and walking/bicycling (5 categories).

†Excluding men and women with diagnosed coronary heart disease or heart failure at baseline.

‡Standard drinks = 12 g alcohol. One standard drink corresponds to approximately 4 cl liquor, 8 cl strong wine, 15 cl wine, 33 cl class III beer (alcohol by volume, >3.5%), 50 cl class II beer (2.8−3.5%), or 66 cl class I beer (<2.25%).

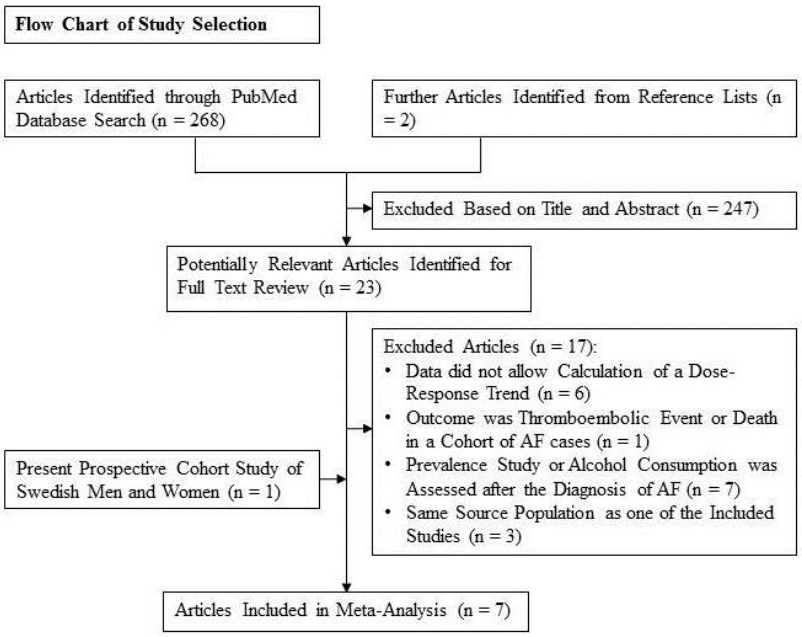
§Median values in parenthesis.

¶*P* for trend across categories of alcohol consumption among current drinkers using the median consumption in each category as a continuous variable.

Dose-response meta-analysis

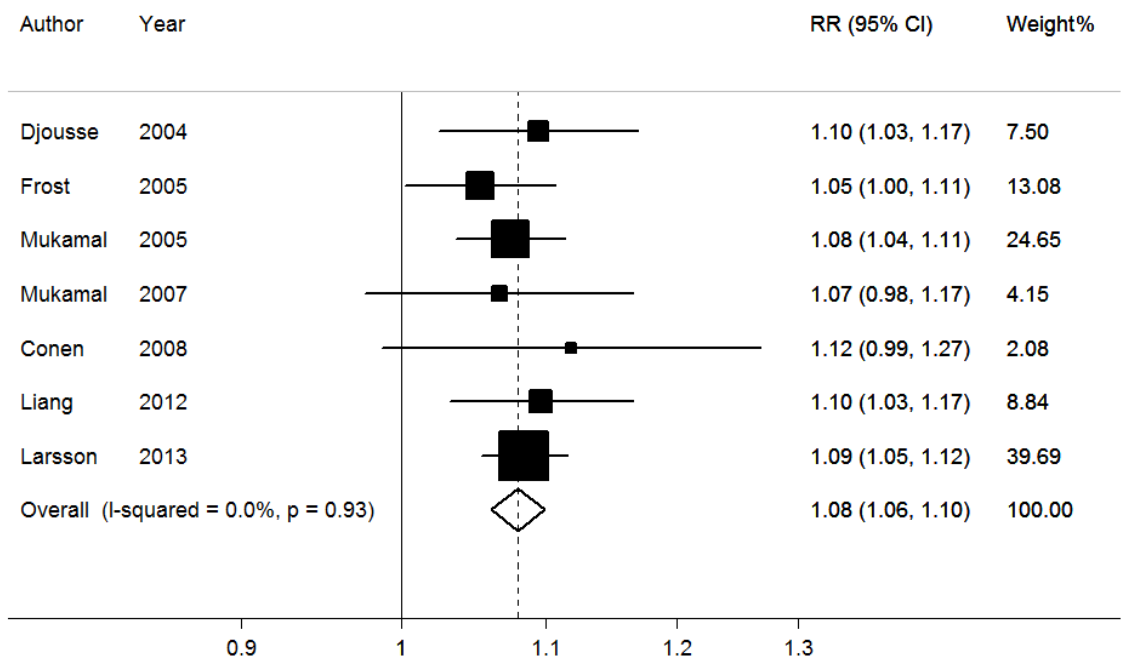
Seven prospective studies, including the two Swedish cohort studies (COSM and SMC), were included in the meta-analysis (Figure 6). Combined these studies contributed 12,554 cases of AF. Three studies were conducted in the United States, 3 studies in Europe, and one study included participants from 40 countries. Alcohol consumption was assessed through a self-administered questionnaire in 6 studies and through interviews in one study [35-37, 98-101] (Figure 5).

Figure 5. Flow chart of study selection.



In a meta-analysis of all studies, we observed a linear dose-response relationship between alcohol consumption and AF risk. All studies reported a positive association, with an overall 8% (6−10%) increase in AF risk for each 1 drink/day increase in alcohol consumption (Figure 6). Excluding our own study, which contributed 40% of the statistical weight, did not change the overall results (RR = 1.08; 95% CI: 1.05-1.10).

Figure 6. Forest Plot of RR of AF per 1 drink/day increment in alcohol consumption



4.2 PAPER II: PHYSICAL ACTIVITY AND THE RISK OF AF IN MEN

Participants were followed up between 1st January 1998 and 31st December 2009. During a median follow-up of 12 years, 4,568 cases of AF were identified in the cohort, which corresponds to 9.6 cases of AF per 1,000 person-years. Baseline characteristics of the study population for the lowest and highest categories of leisure-time exercise and walking/bicycling are shown in Table 5.

After adjustment for other risk factors and excluding men with coronary heart disease or heart failure at baseline, we observed a positive association between leisure-time exercise (high-moderate intensity physical activity) at age 30 and risk of AF. Men who engaged in exercise for five hours or more per week at age 30 had a 19% (95% CI: 5%-36%) higher risk of AF compared with men who engaged in exercise for less than one hour per week. Walking/bicycling (low-moderate intensity physical activity) at the age of 30 was not associated with risk of AF. However, walking/bicycling at baseline (mean age 60 years) was inversely associated with risk of AF (RR 0.87; 95% CI: 0.77 to 0.97 for >1 h/day vs almost never) and the association was similar after excluding men with previous coronary heart disease or heart failure at baseline (Table 6). To investigate how the amount of leisure-time exercise throughout life influences the risk of developing AF, we categorized the population into five groups: Group 1 (reference group): exercise <1 h/week at age 30 and at baseline; Group 2: exercise >5 h/week at age 30 and <1 h/week at baseline; Group 3: exercise >5 h/week at age 30 and at baseline; Group 4: exercise: <1/week at age 30 and >5 h/week at baseline; and Group 5: exercise 1-5 h/week at age 30 and at baseline. A statistically

significant association between leisure-time exercise and risk of AF was only observed among men who had a high level of exercise at age 30 years (>5 h/week) and became inactive at an older age (exercise <1 h/week at baseline) (Group 2). This group had a RR of 1.49 (95% CI: 1.14-1.95) to develop AF compared with Group 1 (exercise <1 h/week at age 30 and at baseline).

Table 5. Age-standardized baseline characteristics for the lowest and highest categories of leisure-time exercise and walking/bicycling in the cohort of Swedish men

Characteristic	Exercise at age 30		Exercise at baseline		Walking/bicycling at age 30		Walking/bicycling at baseline	
	<1 h/wk	>5 h/wk	<1 h/wk	>5 h/wk	Almost never	>1 h/day	Almost never	>1 h/day
Age, mean (years)	57.1	60.9	57.9	63.6	55.9	62.8	59.9	62.8
Height, mean (cm)	177	178	177	177	177	177	177	177
BMI, mean (kg/m^2)	25.9	25.9	26.3	26.2	26.1	25.9	26.5	25.5
Post-secondary education (%)	13.2	14.7	13.7	10.7	14.8	12.7	14.2	12.5
Current smoking (%)	27.5	23.9	30.8	23.2	29.6	25.8	32.7	25.0
Aspirin use (%)	36.9	35.0	37.5	34.1	37.2	35.8	38.4	34.4
History of CHD or heart failure (%)	8.1	8.9	9.4	8.5	10.0	8.9	10.7	8.2
History of hypertension (%)	24.0	21.5	26.2	22.0	26.1	23.6	27.8	21.6
History of type 2 diabetes (%)	9.7	7.8	10.8	8.4	10.8	8.7	12.0	8.2
Family history of MI (%)	14.0	15.7	14.9	18.2	15.6	15.3	15.6	15.1
Alcohol intake, mean (g/day)	9.8	10.7	10.2	10.8	10.4	10.1	10.7	9.9

Table 6. Relative risks of AF by leisure-time exercise and walking/bicycling at age 30 years and at baseline.

Variable	Cases*	Person-years	Age-adjusted RR	Multivariable RR†	Multivariable RR†,‡
Exercise at age 30 years (h/wk)					
<1	499	69,469	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	695	83,297	1.06 (0.94-1.19)	1.07 (0.95-1.20)	1.08 (0.95-1.22)
2-3	1,267	140,057	1.02 (0.92-1.14)	1.04 (0.93-1.16)	1.06 (0.94-1.20)
4-5	619	63,208	1.07 (0.95-1.20)	1.09 (0.96-1.23)	1.13 (0.98-1.29)
>5	790	70,719	1.15 (1.02-1.29)	1.17 (1.03-1.32)	1.19 (1.05-1.36)
P for trend			0.11	0.01	0.008
Exercise at baseline (h/wk)					
<1	821	97,499	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	740	86,712	0.92 (0.83-1.02)	0.96 (0.86-1.06)	0.98 (0·87-1.10)
2-3	1,369	140,318	0.90 (0.83-0.98)	0.97 (0.89-1.07)	1.01 (0·91-1.12)
4-5	582	55,875	0.83 (0.75-0.93)	0.91 (0.81-1.02)	0.96 (0·84-1.09)
>5	802	64,638	0.90 (0.81-0.99)	1.00 (0.90-1.12)	1.05 (0.92-1.18)
P for trend			0.01	0.76	0.60
Walking/bicycling at age 30 years					
Almost never	259	38,662	1.00 (reference)	1.00 (reference)	1.00 (reference)
<20 min/day	717	96,153	1.02 (0.89-1.18)	1.03 (0.89-1.19)	1.08 (0.92-1.26)
20-40 min/day	1,151	134,281	0.93 (0.81-1.07)	0.96 (0.84-1.10)	0.98 (0.84-1.15)
40-60 min/day	786	76,069	0.98 (0.85-1.13)	0.99 (0.86-1.15)	1.03 (0.88-1.21)
>1 hour/d	1,223	101,287	1.04 (0.91-1.20)	1.04 (0.90-1.20)	1.08 (0.93-1.27)
P for trend			0.30	0.45	0.35
Walking/bicycling at baseline					
Almost never	603	59,085	1.00 (reference)	1.00 (reference)	1.00 (reference)
<20 min/day	1,011	112,429	0.90 (0.81-1.00)	0.96 (0.86-1.06)	0.96 (0.85-1.08)
20-40 min/day	1,216	133,991	0.83 (0.75- 0.91)	0.89 (0.80-0.99)	0.90 (0.80-1.01)
40-60 min/day	740	68,753	0.87 (0.78-0.97)	0.95 (0.85-1.07)	0.97 (0.86-1.11)
>1 h/day	851	79,369	0.79 (0.71-0.87)	0.87 (0.77-0.97)	0.88 (0.77-0.998)
P for trend			<0.0001	0.03	0.09

*The sum does not add up to the total owing to missing data for the exposure variable.

†Multivariable models were adjusted for age, education, smoking status and pack years of smoking, BMI, diabetes, history of hypertension, history of CHD or heart failure, family history of myocardial infarction, aspirin use, and alcohol consumption. Leisure-time exercise and walking/bicycling were mutually adjusted in the multivariable model.

‡Excluding men with previous coronary heart disease or heart failure at baseline.

4.3 PAPER III: PHYSICAL ACTIVITY AND THE RISK OF AF IN WOMEN

During a median follow-up of 12 years (10th percentile 7.5 years; 90th percentile 12.0 years, 402,369 person-years), 2,915 cases of AF were diagnosed in the cohort, which corresponds to 7.2 cases of AF per 1,000 person-years. The baseline characteristics of the study population according to leisure-time exercise and walking/bicycling are presented in table 7.

Table 7. Baseline characteristics* of participants of the Swedish Mammography Cohort by categories of exercise and walking/bicycling at study entry

	Exercise at study entry (h/wk)				Walking/bicycling at study entry (min/d)			
Characteristics	<1	1	2-3	≥4	Almost never	<20	20-39	≥40
Age, mean (years)	61.1	60.3	61.2	62.6	64.0	60.5	60.8	62.0
Height (cm)	164.7	164.8	164.9	164.6	164.2	164.8	165.0	164.6
BMI, mean (kg/m^2)	25.7	25.3	24.9	24.4	26.1	25.5	24.9	24.6
Post-secondary education (%)	18.1	20.2	20.3	17.9	14.9	19.0	21.2	18.1
Current smoking (%)	29.7	23.2	20.2	22.2	32.1	25.1	21.4	22.0
History of hypertension (%)	23.4	21.9	20.4	19.1	25.5	21.8	20.5	19.4
History of type 2 diabetes (%)	4.9	3.9	3.7	4.2	6.5	4.3	3.6	3.9
History of CHD or heart failure (%)	5.6	4.7	3.9	3.7	6.9	5.0	4.0	3.7
Family history of MI(%)	17.4	17.2	16.5	18.0	19.3	17.8	17.3	16.5
Alcohol intake, mean (g/day)	5.4	5.3	5.3	5.5	5.4	5.3	5.5	5.3

*Age-standardized to the age distribution of the study population at study entry.

There was no association between risk of AF and leisure-time exercise or walking/bicycling at age 30 years. The risk of AF was inversely associated with leisure-time exercise at baseline with a trend from lowest to highest category, but only women in the highest category (≥4 h/week) had a statistically significant risk reduction (RR 0.85; 95% CI: 0.75 to 0.95) compared with women in the lowest category (<1 h/week) (Table 8). Walking/bicycling at

baseline was also inversely associated with risk of AF. Compared with women who almost never walked or bicycled, women who walked or bicycled 20-39 min/day and ≥40 min/day had a 14% and 19% lower risk of AF, respectively. The association between walking/bicycling and leisure-time exercise at baseline was not modified by previous CHD or heart failure (P for interaction walking/bicycling = 0.60 and P for interaction leisure-time exercise = 0.39).

Table 8. Relative risk (95% confidence interval) of atrial fibrillation by categories of exercise and walking/bicycling in the Swedish Mammography Cohort, 1998–2009

	Cases*	Age-adjusted RR	Multivariable RR†
Exercise at baseline (h/week)			
<1	555	1.00 (reference)	1.00 (reference)
1	564	0.85 (0.75-0.95)	0.89 (0.79-1.00)
2–3	888	0.84 (0.75-0.93)	0.92 (0.82-1.02)
≥4	601	0.75 (0.67-0.84)	0.85 (0.75-0.95)
P for trend		<0.0001	0.02
Walking/bicycling at baseline (min/day)			
Almost never	421	1.00 (reference)	1.00 (reference)
<20	524	0.88 (0.78-1.01)	0.94 (0.82-1.07)
20–39	880	0.77 (0.68-0.89)	0.86 (0.76-0.97)
≥40	937	0.71 (0.63-0.80)	0.81 (0.72-0.92)
P for trend		<0.0001	0.0002

*The sum does not add up to the total owing to missing data for the exposure variable.

†Multivariable models were adjusted for same as table 6 except for adjustment of leisure-time exercise and walking/bicycling.

4.4 PAPER IV: LIFESTYLE FACTORS AND THE RISK OF AF

In both men and women, the risk of AF decreased in a dose–response manner with increasing number of healthy lifestyle factors (Table 9). Compared with men and women with no indicator of a healthy lifestyle, those with all four factors had a 50% (95% CI: 36% to 61%) lower risk of AF after adjustment for other risk factors.

Table 9. Relative risks of atrial fibrillation according to number of any healthy lifestyle factors among 39,300 men in the Cohort of Swedish Men and 33,090 women in the Swedish Mammography Cohort, 1998-2009

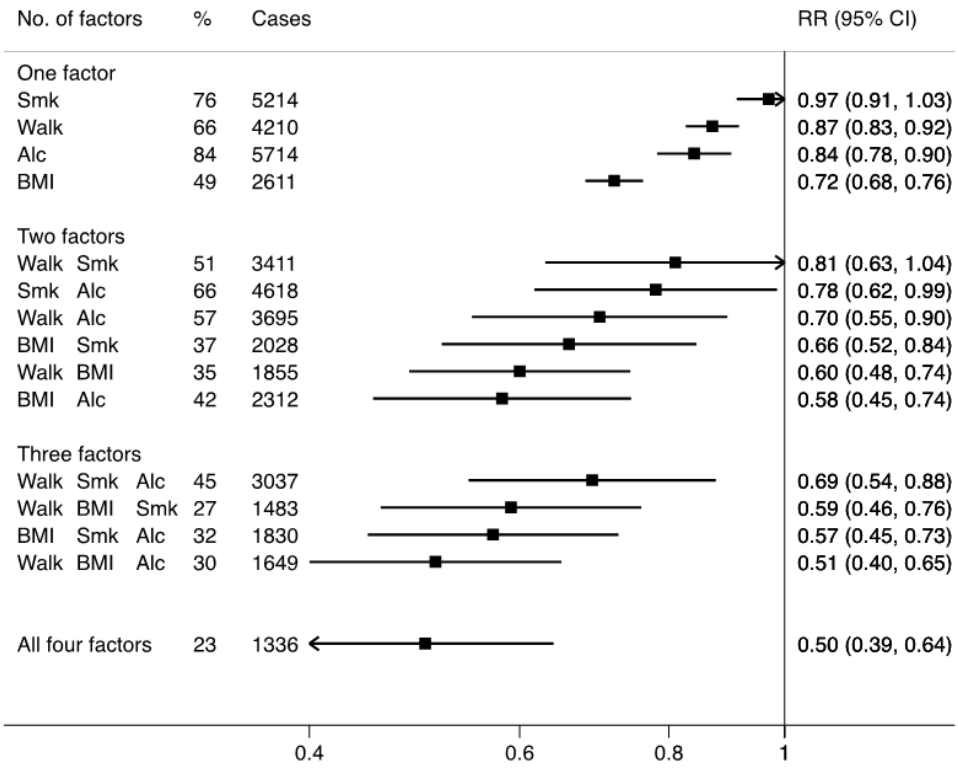
	Men and women combined			Men			Women		
No. of healthy lifestyle factors	No. of cases	Model 1 RR (95% CI)*	Model 2 RR (95% CI)†	No. of cases	Model 1 RR (95% CI)*	Model 2 RR (95% CI)†	No. of cases	Model 1 RR (95% CI)*	Model 2 RR (95% CI)†
0	131	1.00 (reference)	1.00 (reference)	113	1.00 (reference)	1.00 (reference)	18	1.00 (reference)	1.00 (reference)
1	768	0.83 (0.69-1.00)	0.84 (0.69-1.01)	626	0.85 (0.69-1.03)	0.85 (0.69-1.04)	142	0.73 (0.45-1.20)	0.73 (0.45-1.21)
2	2,051	0.74 (0.62-0.89)	0.75 (0.62-0.90)	1,373	0.75 (0.62-0.91)	0.76 (0.62-0.92)	678	0.66 (0.41-1.05)	0.66 (0.41-1.07)
3	2,453	0.63 (0.52-0.75)	0.64 (0.53-0.77)	1,354	0.64 (0.52-0.77)	0.64 (0.53-0.78)	1099	0.55 (0.34-0.88)	0.57 (0.36-0.92)
4	1,160	0.50 (0.41-0.60)	0.51 (0.42-0.61)	562	0.53 (0.43-0.65)	0.53 (0.43-0.65)	598	0.42 (0.26-0.67)	0.44 (0.27-0.71)
P for trend		<0.0001	<0.0001		<0.0001	<0.0001		<0.0001	<0.0001

*Model 1 adjusted for age and sex.

†Model 2 adjusted for age, sex, height, education, family history of myocardial infarction before 60 years of age, history of diabetes, history of cardiac disease, and leisure-time exercise.

We next examined the separate and joint association of different combinations of the four healthy lifestyle factors with AF risk (Figure. 7). Low BMI, regular walking/bicycling, and light or no alcohol consumption was associated with a statistically significant reduced risk of AF, with the most pronounced reduction in AF risk observed for a low BMI. Abstinence from smoking was not significantly associated with risk of AF. Combinations that included BMI conferred the greatest reduction in AF risk.

Figure 7. Multivariable RR and 95% CI of AF according to different combinations of four healthy lifestyle factors



5 DISCUSSION

5.1 MAIN FINDINGS AND GENERAL DISCUSSION

The main result of this theses based on findings from two large population based Swedish cohort studies show that modifiable lifestyle factors influence the risk of AF. These findings are important in order to create better preventive programs to prevent or delay the onset of AF. AF has a variety of negative consequences that are described earlier in this thesis and prevention is of the essence. Praestat cautela quam medela (latin) (Prevention is better than cure) (Often attributed to Marcus Tullius Cicero; January 106 BC – 7 December 43 BC)

Study I showed that even a moderate intake of alcohol (1-3 drinks / day) was associated with an increased risk. In line with previous studies we found that binge drinking further increased the risk for AF. The risk of developing AF persisted even after excluding the binge drinkers in both high and moderate alcohol consumers. The association between alcohol consumption and AF risk was similar in men and women. This finding was deviant from previous studies which have shown that women are generally more sensitive to the harmful effects of alcohol [29]. The overall result of alcohol as a risk factor for AF was confirmed in our dose-response meta-analysis of 7 studies (including our own cohort study) which showed a positive association, with an overall 8 % (6-10%) increase in AF risk per 1 drink/day increment in alcohol consumption.

In study II and III we investigated the complex association between physical activity and risk of AF. Men who reported ≥5 hours of leisure-time exercise per week at age 30 had a 19 % increased risk of AF later in life compared with men who exercised less than 1 hour per week at that age. The risk of AF was even greater (RR 1.49) among men who exercised ≥5 hours per week at age 30 years, and were inactive at older age. On the other hand our data showed that low intensity physical activity like walking and bicycling was associated with a decreased risk of AF in both middle-aged and elderly men and women. In women, we could not observe any increased risk of AF in any age group with more intense physical activity like leisure-time exercise. Contrary, we found a small risk reduction in middle-age and elderly women at our highest categories of leisure time exercise (>5 hours/week). Our studies support the theory of a more complex association between physical activity and risk of AF. How physical activity influence the risk depends on several factors. Some of these factors include intensity of physical activity, duration of physical activity, age at physical activity measurement and possibly gender. The conflicting results in previous studies may depend on the fact that these factors have not been separated. Athletes and young to middle-aged men with a history of high levels of vigorous physical activity have an increased risk of AF [24, 48-50, 102, 103]. On the other hand, studies done on individuals of older age showed that physical activity reduced or had no effect on the incidence of AF[52, 104]. Women have been far less studied and most studies on athletes have included exclusively men or a smaller portion of women. Azerbal et al reported that physical activity decreased the risk of AF among middle age and elderly women [105]. Everett et al and Thelle et al studied middle-aged women from the general population and did not find any association between physical

activity and the increased risk of AF, instead there was a tendency for a small risk reduction [106, 107]. Andersen et al and Myrstad at el tried to determine if endurance exercise influence the risk of AF in women. They found no significant associations but the point estimate suggested that high levels of endurance exercise increase the risk of AF but both studies had limited number of end-points which decreased the power of the studies and resulted in a very wide CI [102, 108]. Wilhelm et al observed a sex difference for atrial and ventricular remodeling and autonomic tone with respect to endurance training. After a comparable amount of exercise, male athletes have more structural remodeling with left atrial dilation, larger LV mass index as well as greater relative wall thickness and sympatho-vagal balance [109]. All these factors could influence the risk of developing AF. Endurance sports were not too long ago considered inappropriate for women and they were not allowed to participate in endurance sport events. The first woman to run Boston Marathon was Bobby Gibb in 1966 and she had to wear a hooded sweatshirt in order to sneak into the race. The first women marathon race in the Olympic Games was held in 1984. Long-distance running has become popular among women just in the last one to two decades. There are still far fewer women than men who engage in high-intensity endurance training. Only a small fraction of men who engaged in high intensity endurance training over a prolonged period of time developed AF. In our study on men (study II) the population attributable risk for the exposure, lesiure-time exersice, was 1.7%. Studies have shown that 10-30 years of accumulated vigorous physical activity is needed to increase the risk of AF [110, 111]. Since AF is most likely to develop after extended periods of vigorous physical activity and years after the exposure we may not yet be able to identify any increased risk of AF among women due to insufficient follow-up time, low number of adequately exposed individuals leading to low number of end-points.

Our studies together with previous studies suggest a U-shaped relationship between physical activity and the risk of AF in men [112]. However, there are no data to indicate that this would lead to premature death in this group. If there is any true gender difference between the association of AF and physical activity it remains unresolved.

Finally, we investigated the combined impact of four healthy lifestyle factors (BMI <25 kg/m^2, regular walking/bicycling ≥20 min/day, no or light alcohol consumption and no smoking) on risk of AF. A combination of all four healthy lifestyle factors was associated with a halving of the risk of AF. In this study the modifiable life style factor that was most strongly associated with a risk reduction was a BMI of less than 25 kg/m^2. We observed no statistical significant association between smoking and risk of AF. AF is associated with an up to fivefold increased risk of stroke, it is associated with increased mortality and is one of the most common reasons for hospital admission [113, 114]. In view of the severe consequences of AF and significant economic burden that it inflicts on society it is important to prevent the onset of AF. The result of this study highlights the great potentials of preventive medicine and it is in agreement with previous studies. The ARIC study, which compared participants with optimal and borderline risk factors with participants with elevated risk factors for AF saw that the RRs (95% CI) of AF for those with borderline and optimal

risk profiles were 0.50 (0.44–0.57) and 0.33 (0.23–0.47), respectively, compared to those with an elevated risk profile. An optimal risk profile was defined as no history of cardiac disease; systolic blood pressure <120 mmHg, diastolic blood pressure <80 mmHg, and no use of antihypertensive medication; fasting serum glucose <100 mg/dL, no use of anti-diabetic medication, and no history of DM, BMI <25 kg/m2 and never smoker [115]. The Framingham Heart Study reported that prevalent coronary heart disease, hypertension, DM, and smoking could explain 44% of the burden of AF in men and 58% of the burden in women [57]. In the ARREST-AF trial an aggressive risk factor modification on multiple risk factors reduced the risk of recurrent AF after catheter ablation [69].

5.2 METHODOLOGY

All the studies in this thesis are prospective population cohort studies. Cohort studies are observational studies and in general they are hypothesis-generating and describe association between exposure and disease and not the cause of the disease. However, if properly conducted several cohort studies and meta-analysis combined could suggest causal relationship between exposure and outcome.

5.2.1 Information bias

Misclassification of exposure

Measurements of the exposure variables; alcohol consumption, physical activity, BMI (weight and height) and smoking were self-reported in a questionnaire and some of the information like physical activity at age 15 and 30 was reported retrospectively at baseline in 1997 were the participates had a mean age of 60 years. A limitation of information gathered by self-reported questionnaire is that the participants do not recall the exact level of the exposure for example leisure-time exercise. They could overestimate or underestimate the true level. This could lead to misclassification of exposure because of incorrect recall and reporting. Measurements of leisure-time exercise and walking/bicycling were done in the questionnaire with pre-defined categories and it is not a precise and objective measurement rather more an activity-ranking. The participants should however be able to classify themselves with rather good precision between the lowest and highest categories (<1 hour/week vs. >5 hour/week) even when asked to do that retrospectively. Another limitation and potential misclassification was that exposures of interest were only measured once and this could lead to measurement errors if participants changed their lifestyle during follow-up. Because information on exposures was gathered before diagnosis of AF, any misclassification would be expected to be unrelated to the outcome. Non-differential misclassification would most likely have attenuated rather than exaggerated the true association between exposure and AF in our studies.

Misclassification of outcome

In all studies in this thesis, outcome of AF was collected by computerized linkage of the two cohorts (COSM and SMC) to the Swedish NPR which allowed for an almost complete follow-up. The incidence of AF may be underestimated because the cases in the Swedish NPR are gathered from in-hospital specialist care and from 2001 also from out-hospital specialist care. We cannot rule out that some of the non-cases had asymptomatic AF that was not diagnosed since there is no screening program in Sweden for detection of AF in asymptomatic patients. We have no reason to believe that different exposures of physical activity or alcohol should influence if the AF episode is symptomatic or not. The misclassification of outcome should therefore be non-differential.

5.2.2 Selection bias

Selection bias is limited in a prospective cohort study since exposed and unexposed participants should be free of the outcome off interest at start of follow-up. We cannot exclude the presence of selection bias since our results are based on questionnaires and the volunteers answering the questionnaire may not represent a cross-section of women and men in Sweden. Since AF could have been present but not diagnosed at start of follow-up we did a sensitivity analysis where we excluded AF cases during the first 3 and 5 years of follow-up in study IV and during the first year in study II. The result remained essentially the same. Selection bias could also have occurred if there is a difference in the completeness of follow-up between exposed and un-exposed individuals. Since follow-up of all individuals was through the Swedish NPR it allowed for an almost complete and equal follow-up, it is unlikely that the health seeking behavior is different among exposed and unexposed but we cannot rule it out and that could create a selection bias.

5.2.3 Confounding

In the four studies, we attempted to control for confounding by adjusting for other risk factors. In addition, we excluded participants with prior CHD or heart failure since they may have changed their physical activity levels and CHD and heart failure influence the risk of AF. Unmeasured confounding cannot be excluded and may have contributed to the observed results. We did not have information about obstructive sleep apnea or chronic obstructive pulmonary disease which could both affect the physical activity levels and the risk of AF.

5.2.4 Publication bias

Publication bias means that there is a tendency for small studies with negative results to remain unpublished. This type of bias may be introduced if only results from published studies are used in the meta-analysis. The presence of publication bias can be assessed by a variety of graphical and statistical methods. In study IV we used Egger's test [116]. We found no evidence of publication bias but test for publication bias have low statistical power, especially when the number of studies are small ($n<10$).

6 CONCLUSION

1. Alcohol consumption is associated with a increased risk of AF. Moderate consumption of alcohol, which seems to lowers the risk of other cardiovascular diseases, was enough to slightly increase the risk of AF.

2. High levels of vigorous intensity physical activity at younger age increase the risk of AF in men while more moderate intensity decreases the risk at least in older men.

3. Regular physical activity is associated with a reduced risk of AF in women. Moderate amount of daily physical activity was sufficient to have a significant risk reduction. High levels of leisure-time exercise were not a risk factor for AF in women as previously described in men.

4. A combination of four healthy lifestyle factors (BMI <25 kg/m^2, regular walking or bicycling ≥20 min/day, no or light alcohol consumption and no smoking) was associated with a halving of the risk of AF. The modifiable life style factor that was most strongly associated with a risk reduction was a BMI of less than 25 kg/m^2.

7 FUTURE PERSPECTIVES

Regular physical activity promotes health and reduces all-cause mortality [117]. However some individuals who are performing long-time vigorous physical activity will develop AF. Individual susceptibility factors are needed to be found. Further studies are needed to investigate the risk of AF in female endurance athletes. So far we have not been able to establish any association between long-time vigorous physical activity and the risk of AF in females. The question remains if it is a true gender difference or if it is just methodological shortcomings and lack of power in previous studies.

Physical activity has several positive effects on several risk factors for stroke, and there is a question if patients with exercise-induced AF render the same stroke risk as other AF patients and if CHA2DS2-VASc score is best for estimating stroke risk.

It is known from previous studies that there are ethnic differences in the cardiac adaptation to intense physical activity [118]. Genetic markers for increased risk of exercise-induced AF are not yet found and research is needed in order to localize them.

It is still unclear what advice to give to athletes who develop AF. Detraining could reduce the ventricular arrhythmias in athletes [119]. In an animal model (rats) training increased the AF inducibility and detraining returned it to baseline levels [120]. If detraining will do the same thing for human athletes is still unclear and what level of physical activity is the best is also unknown.

The exact mechanisms by which regular high intensity exercise promotes the development of AF is unclear. Mechanisms that could be contributing include atrial enlargement, inflammatory changes, vagal enhancement, and structural alterations in the atria. Further research is needed to determine the exact mechanism.

Today we are not able to establish specific mechanisms of AF for an individual patient. Current catheter based ablation strategies are mainly based on the pattern of AF (paroxysmal vs persistent). Destruction of atrial tissue with the purpose of curing AF could lead to complications such as ablation induced arrhythmias. More research is needed to identify new modifiers of AF and to better understand how to intervene with reversible health modifiers. As our knowledge about causes and pathophysiological mechanisms grows more individual tailored treatments will be developed and we will have better outcomes and hopefully less side effects.

"How much longer do I have before I have to change to a healthy lifestyle?"

8 SAMMANFATTNING (SUMMARY IN SWEDISH)

Förmaksflimmer är den vanligaste hjärtrytmrubbningen av klinisk betydelse och förekomsten av förmaksflimmer beräknas hos den vuxna befolkningen var omkring 3 %. Förmaksflimmer kan ge en mängd olika symptom samt ökar risk att dö i förtid vilket delvis kan förklaras av en ökad förekomst av hjärtsvikt och stroke. Det finns ett flertal riskfaktorer och medicinska tillstånd som förknippas med förmaksflimmer. Exempel på dessa är hög ålder, manligt kön, hjärtsvikt, hjärtklaffsjukdom, hjärtinfarkt, kronisk obstruktiv lungsjukdom, sömnapné, kronisk njursjukdom, sköldkörtelsjukdom, rökning, alkohol och fysisk aktivitetsnivå och genetiska faktorer. En del riskfaktorer är modifierbara. Syftet med denna avhandling var att undersöka hur modifierbara livsstilsfaktorer, och då särskild alkoholkonsumtion och fysisk aktivitet, påverkar risken för förmaksflimmer.

I **studie I** undersökte vi sambandet mellan alkoholkonsumtion och risken för förmaksflimmer i en prospektiv kohortstudie av svenska män och kvinnor (n = 79 019). Vid gjorde även en meta-analys av tidigare genomförda prospektiva studier (n = 7). Studien visade att alkoholkonsumtionen är förknippat med en ökad risk för förmaksflimmer hos både män och kvinnor. Även måttligt intag, vilket anses minskar risken för andra hjärt-kärlsjukdom, var förknippat med en ökad risk för förmaksflimmer.

I **studie II** undersökte vi sambandet mellan fysisk aktivitet vid olika åldrar och av olika typ med risk för förmaksflimmer i en stor (n = 48 850) manliga kohort. En hög nivå av motion (måttlig intensiv till högintensiv fysisk aktivitet) hos yngre män var förknippad med en ökad risk för förmaksflimmer. Däremot var promenader/cykling (låg intensiv till måttlig intensiv fysisk aktivitet) vid en högre ålder, förknippat med en minskad risk.

I **studie III** utvärderade vi sambandet mellan fysisk aktivitet vid olika åldrar och av olika typ med risk att utveckla förmaksflimmer i en stor (n = 39 227) kvinnliga kohort. Regelbunden fysisk aktivitet var förknippad med en minskad risk för förmaksflimmer hos kvinnor. Måttlig mängd daglig fysisk aktivitet var tillräckligt för att minska risken hos medelålders och äldre kvinnor. Höga nivåer av motion (måttlig intensiv till högintensiv fysisk aktivitet) var till skillnad vad vi fann hos män inte en riskfaktor för förmaksflimmer hos kvinnor.

I **studie IV** undersökte vi den gemensamma effekten av fyra modifierbara livsstilsfaktorer på risken att utveckla förmaksflimmer hos både män och kvinnor. En halvering av risken att utveckla förmaksflimmer såg hos dem som hade all fyra hälsosamma livsstilsfaktorer (BMI <25 kg/m^2, regelbunden motion $\geq$20 min/dag, ingen eller lätt alkoholkonsumtion och ingen rökning).

Sammanfattning: Alkoholkonsumtionen är förknippat med en ökad risk för förmaksflimmer. Högintensiv fysisk aktivitet kan öka risken för förmaksflimmer hos yngre män medan låg till måttlig intensiv fysisk aktivitet minskar risken hos både män och kvinnor. Höga nivåer av intensiv fysisk aktivitet var inte en riskfaktor för förmaksflimmer hos kvinnor. En hälsosam livsstil kan avsevärt minska risken för förmaksflimmer hos både män och kvinnor.

9 ACKNOWLEDGMENTS

I wish to express my sincere gratitude to all of you who have helped, supported and inspired me during the work with my thesis. Some have done it consciously others more subconsciously. I wish to express my gratitude to:

All the women and men in Swedish Mammography Cohort and *Cohort of Swedish Men* who took their time answering the questionnaire.

Mats Jensen-Urstad my principal supervisor for all your support, in variety of different ways, during these years. For good advice, not just about scientific and clinical questions but also about life in general. Special thanks for your patience with me and for letting me choose my own scientific path.

Susanna Larsson my co-supervisor for your tremendous generosity, for always sharing your time and knowledge. Thank you for being available 24/7 and giving me rapid feedback. I am deeply grateful to you for showing me how a true epidemiologist works. Without your help and support I would not have been able to complete this thesis.

Per Insulander and *Hamid Bastani* my co-supervisors for your encouragement and kindness and for always opening your homes and creating a welcoming atmosphere. You are true gentlemen.

Alicja Wolk my co-author and the "mother" of Swedish Mammography Cohort and Cohort of Swedish Men for your generosity and for believing in me six years ago, when I first approached your research group.

Karolinska Institutet and specially to *Jan Bolinder,* head of Department of Medicine, Huddinge, Karolinska Institutet and to *Anastasia Urban,* educational administrator at Department of Medicine Huddinge for a great doctoral education and for your support.

Past and present heads of Department of Cardiology, Karolinska University Hospital, *Cecilia Linde*, *Fredrik Gadler* and *Frieder Braunschweig* for kind support and giving me the opportunity to take time off for research.

Past and present electrophysiology technicians *Linus Holmström* for your friendship and endless discussion about signals, pacing maneuvers and for pushing me to dream bigger dreams. *Christer Wredlert, Anna Grahn*, *Mats Andersson* and *Martin Värild* for your friendship and everyday support. For teaching me the fundamentals in electrophysiology and making my everyday life at work easier and more fun.

Marieann Högman for introducing me to research and showing me how joyful it should be. I still have warm memories from our projects back in the late 90s.

Göran Kennebäck and *Hans Berglund* for once employing me and for your encouraging guidance which helped me to choose electrophysiology.

Past and present colleagues at the electrophysiology lab Karolinska University Hospital, *Jonas Schwieler, Ott Saluveer, Tara Bourke, Anette Jemtrén, Jari Tapanainen, Kristján Guðmundsson, Serkan Sayagi, Zviad Matoshvili* and *Fariborz Tabrizi* my United Nations of Electrophysiologists with different backgrounds and characters but warm hearts and open minds. Thank you for all the support and special thanks to *Tara Bourke* for your help with linguistic revision of this thesis.

Bita Sadigh for your witty comments and your friendship.

Niclas Johansson my mentor in this project and close friend who had travelled this road a few years before me, for your encouragement.

Carina Carnlöf my Phd-student companion. It is great to have someone like you to share setbacks and success with and thank you for all the tips on student discounts.

My parents *Milos Drča* and *Ružica Drča* for your unconditional support and endless love.

My loving family. My beautiful wife *Anna Drča* for love and endurance for **always** reminding me what is truly important in life. *Miriam Drča, Baltasar Drča* and *Sakarias Drča* my wonderful children for all the joy and happiness you give me.

Insamlingsstiftelsen Kvinnor och Hälsa for financial support.

10 REFERENCES

1. Camm, A.J., et al., *Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).* Eur Heart J, 2010. **31**(19): p. 2369-429.

2. Kirchhof, P., et al., *Outcome parameters for trials in atrial fibrillation: recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association.* Europace, 2007. **9**(11): p. 1006-23.

3. Waldo, A.L. and G.K. Feld, *Inter-Relationships of Atrial Fibrillation and Atrial Flutter: Mechanisms and Clinical Implications.* Journal of the American College of Cardiology, 2008. **51**(8): p. 779-786.

4. Knight, B.P., et al., *Electrocardiographic differentiation of atrial flutter from atrial fibrillation by physicians.* Journal of Electrocardiology. **32**(4): p. 315-319.

5. Kirchhof, P., et al., *2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS.* Eur Heart J, 2016. **37**(38): p. 2893-2962.

6. Calkins, H., et al., *2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design.* A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society, 2012. **14**(4): p. 528-606.

7. Kirchhof, P., et al., *Personalized management of atrial fibrillation: Proceedings from the fourth Atrial Fibrillation competence NETwork/European Heart Rhythm Association consensus conference.* Europace, 2013. **15**(11): p. 1540-56.

8. Fabritz, L., et al., *Expert consensus document: Defining the major health modifiers causing atrial fibrillation: a roadmap to underpin personalized prevention and treatment*. Nat Rev Cardiol, 2016. **13**(4): p. 230-7.

9. Haim, M., et al., *Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation.* J Am Heart Assoc, 2015. **4**(1): p. e001486.

10. Friberg, L. and L. Bergfeldt, *Atrial fibrillation prevalence revisited.* J Intern Med, 2013. **274**(5): p. 461-8.

11. Heeringa, J., et al., *Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study.* Eur Heart J, 2006. **27**(8): p. 949-53.

12. Wynn, G.J., et al., *The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification.* Europace, 2014. **16**(7): p. 965-72.

13. Wolf, P.A., R.D. Abbott, and W.B. Kannel, *Atrial fibrillation as an independent risk factor for stroke: the Framingham Study.* Stroke, 1991. **22**(8): p. 983-8.

14. Steinberg, B.A., et al., *Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial.* Eur Heart J, 2015. **36**(5): p. 288-96.

15. Vanassche, T., et al., *Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES.* Eur Heart J, 2015. **36**(5): p. 281-7a.

16. January, C.T., et al., *2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society.* J Am Coll Cardiol, 2014. **64**(21): p. e1-76.

17. Benjamin, E.J., et al., *Impact of atrial fibrillation on the risk of death: the Framingham Heart Study.* Circulation, 1998. **98**(10): p. 946-52.

18. Andersson, T., et al., *All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study.* Eur Heart J, 2013. **34**(14): p. 1061-7.

19. Ott, A., et al., *Atrial fibrillation and dementia in a population-based study. The Rotterdam Study.* Stroke, 1997. **28**(2): p. 316-21.

20. Krahn, A.D., et al., *The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study.* Am J Med, 1995. **98**(5): p. 476-84.

21. Benjamin, E.J., et al., *Prevention of atrial fibrillation: report from a national heart, lung, and blood institute workshop.* Circulation, 2009. **119**(4): p. 606-18.

22. Shah Md, A.D., F.M. Merchant Md, and D.B. Delurgio Md, *Atrial Fibrillation and Risk of Dementia/Cognitive Decline.* J Atr Fibrillation, 2016. **8**(5): p. 1353.

23. Larsson, S.C., et al., *Incidence of atrial fibrillation in relation to birth weight and preterm birth.* Int J Cardiol, 2015. **178**: p. 149-52.

24. Mont, L., et al., *Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individuals.* Europace, 2008. **10**(1): p. 15-20.

25. Schnabel, R.B., et al., *50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study.* Lancet, 2015. **386**(9989): p. 154-62.

26. Gronbaek, M., *The positive and negative health effects of alcohol- and the public health implications.* J Intern Med, 2009. **265**(4): p. 407-20.

27. Piano, M.R., *Alcoholic cardiomyopathy: incidence, clinical characteristics, and pathophysiology.* Chest, 2002. **121**(5): p. 1638-50.

28. Rehm, J., et al., *Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders.* Lancet, 2009. **373**(9682): p. 2223-33.

29. Roerecke, M. and J. Rehm, *The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis.* Addiction, 2012. **107**(7): p. 1246-60.

30. Roerecke, M. and J. Rehm, *Alcohol consumption, drinking patterns, and ischemic heart disease: a narrative review of meta-analyses and a systematic review and meta-analysis of the impact of heavy drinking occasions on risk for moderate drinkers.* BMC Med, 2014. **12**: p. 182.

31. Tonelo, D., R. Providencia, and L. Goncalves, *Holiday heart syndrome revisited after 34 years.* Arq Bras Cardiol, 2013. **101**(2): p. 183-9.

32. Fernandez-Sola, J., *Cardiovascular risks and benefits of moderate and heavy alcohol consumption.* Nat Rev Cardiol, 2015. **12**(10): p. 576-87.

33. Djoussé, L., et al., *Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham Study.* American Journal of Cardiology. **93**(6): p. 710-713.

34. Frost, L. and P. Vestergaard, *Alcohol and risk of atrial fibrillation or flutter: A cohort study.* Archives of Internal Medicine, 2004. **164**(18): p. 1993-1998.

35. Mukamal, K.J., et al., *Alcohol consumption and risk of atrial fibrillation in men and women: the Copenhagen City Heart Study.* Circulation, 2005. **112**(12): p. 1736-42.

36. Conen, D., et al., *ALcohol consumption and risk of incident atrial fibrillation in women.* JAMA, 2008. **300**(21): p. 2489-2496.

37. Liang, Y., et al., *Alcohol consumption and the risk of incident atrial fibrillation among people with cardiovascular disease.* CMAJ, 2012. **184**(16): p. E857-66.

38. Caspersen, C.J., K.E. Powell, and G.M. Christenson, *Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research.* Public Health Rep, 1985. **100**(2): p. 126-31.

39. Roberts, S.B., et al., *Comparison of the doubly labeled water (2H2(18)O) method with indirect calorimetry and a nutrient-balance study for simultaneous determination of energy expenditure, water intake, and metabolizable energy intake in preterm infants.* Am J Clin Nutr, 1986. **44**(3): p. 315-22.

40. Westerterp, K.R., *Assessment of physical activity: a critical appraisal.* Eur J Appl Physiol, 2009. **105**(6): p. 823-8.

41. Larsson, S.C., et al., *Physical activity, obesity, and risk of colon and rectal cancer in a cohort of Swedish men.* Eur J Cancer, 2006. **42**(15): p. 2590-7.

42. Lee, I.M., et al., *Relative intensity of physical activity and risk of coronary heart disease.* Circulation, 2003. **107**(8): p. 1110-6.

43. Villegas, R., et al., *Physical activity and the incidence of type 2 diabetes in the Shanghai women's health study.* Int J Epidemiol, 2006. **35**(6): p. 1553-62.

44. Wannamethee, S.G. and A.G. Shaper, *Physical activity and the prevention of stroke.* J Cardiovasc Risk, 1999. **6**(4): p. 213-6.

45. Camacho, T.C., et al., *Physical activity and depression: evidence from the Alameda County Study.* Am J Epidemiol, 1991. **134**(2): p. 220-31.

46. Haskell, W.L., et al., *Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association.* Circulation, 2007. **116**(9): p. 1081-93.

47. Wen, C.P., et al., *Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study.* Lancet, 2011. **378**(9798): p. 1244-53.

48. Karjalainen, J., et al., *Lone atrial fibrillation in vigorously exercising middle aged men: case-control study.* BMJ, 1998. **316**(7147): p. 1784-5.

49. Molina, L., et al., *Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study.* Europace, 2008. **10**(5): p. 618-23.

50. Elosua, R., et al., *Sport practice and the risk of lone atrial fibrillation: a case-control study.* Int J Cardiol, 2006. **108**(3): p. 332-7.

51. Heidbuchel, H., et al., *Endurance sports is a risk factor for atrial fibrillation after ablation for atrial flutter.* Int J Cardiol, 2006. **107**(1): p. 67-72.

52. Mozaffarian, D., et al., *Physical activity and incidence of atrial fibrillation in older adults: the cardiovascular health study.* Circulation, 2008. **118**(8): p. 800-7.

53. Wong, C.X., et al., *Obesity and the Risk of Incident, Post-Operative, and Post-Ablation Atrial FibrillationA Meta-Analysis of 626,603 Individuals in 51 Studies.* JACC: Clinical Electrophysiology, 2015. **1**(3): p. 139-152.

54. Wang, T.J., et al., *Obesity and the risk of new-onset atrial fibrillation.* Jama, 2004. **292**(20): p. 2471-7.

55. Tedrow, U.B., et al., *The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (women's health study).* J Am Coll Cardiol, 2010. **55**(21): p. 2319-27.

56. Pathak, R.K., et al., *Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation CohortA Long-Term Follow-Up Study (LEGACY).* Journal of the American College of Cardiology, 2015. **65**(20): p. 2159-2169.

57. Benjamin, E.J., et al., *Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study.* Jama, 1994. **271**(11): p. 840-4.

58. Manolis, A.J., et al., *Hypertension and atrial fibrillation: diagnostic approach, prevention and treatment. Position paper of the Working Group 'Hypertension Arrhythmias and Thrombosis' of the European Society of Hypertension.* J Hypertens, 2012. **30**(2): p. 239-52.

59. Ehrlich, J.R., S.H. Hohnloser, and S. Nattel, *Role of angiotensin system and effects of its inhibition in atrial fibrillation: clinical and experimental evidence.* Eur Heart J, 2006. **27**(5): p. 512-8.

60. Schaer, B.A., et al., *Risk for incident atrial fibrillation in patients who receive antihypertensive drugs: a nested case-control study.* Ann Intern Med, 2010. **152**(2): p. 78-84.

61. L'Allier, P.L., et al., *Angiotensin-converting enzyme inhibition in hypertensive patients is associated with a reduction in the occurrence of atrial fibrillation.* J Am Coll Cardiol, 2004. **44**(1): p. 159-64.

62. National Center for Chronic Disease, P., S. Health Promotion Office on, and Health, *Reports of the Surgeon General*, in *The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General*. 2014, Centers for Disease Control and Prevention (US): Atlanta (GA).

63. Chamberlain, A.M., et al., *Smoking and incidence of atrial fibrillation: results from the Atherosclerosis Risk in Communities (ARIC) study.* Heart Rhythm, 2011. **8**(8): p. 1160-6.

64. Heeringa, J., et al., *Cigarette smoking and risk of atrial fibrillation: the Rotterdam Study.* Am Heart J, 2008. **156**(6): p. 1163-9.

65. Rahman, F., et al., *Trajectories of Risk Factors and Risk of New-Onset Atrial Fibrillation in the Framingham Heart Study.* Hypertension, 2016. **68**(3): p. 597-605.

66. Frost, L., L.J. Hune, and P. Vestergaard, *Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study.* Am J Med, 2005. **118**(5): p. 489-95.

67. Zhu, W., et al., *Association of smoking with the risk of incident atrial fibrillation: A meta-analysis of prospective studies.* Int J Cardiol, 2016. **218**: p. 259-66.

68. Dublin, S., et al., *Diabetes mellitus, glycemic control, and risk of atrial fibrillation.* J Gen Intern Med, 2010. **25**(8): p. 853-8.

69. Pathak, R.K., et al., *Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation: The ARREST-AF Cohort Study.* Journal of the American College of Cardiology, 2014. **64**(21): p. 2222-2231.

70. Fatemi, O., et al., *Impact of intensive glycemic control on the incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes mellitus (from the Action to Control Cardiovascular Risk in Diabetes Study).* Am J Cardiol, 2014. **114**(8): p. 1217-22.

71. Cadby, G., et al., *Severity of OSA is an independent predictor of incident atrial fibrillation hospitalization in a large sleep-clinic cohort.* Chest, 2015. **148**(4): p. 945-52.

72. Gami, A.S., et al., *Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation.* J Am Coll Cardiol, 2007. **49**(5): p. 565-71.

73. Shukla, A., et al., *Effect of Obstructive Sleep Apnea Treatment on Atrial Fibrillation RecurrenceA Meta-Analysis.* JACC: Clinical Electrophysiology, 2015. **1**(1): p. 41-51.

74. Kanagala, R., et al., *Obstructive sleep apnea and the recurrence of atrial fibrillation.* Circulation, 2003. **107**(20): p. 2589-94.

75. Johansson, K., et al., *Longer term effects of very low energy diet on obstructive sleep apnoea in cohort derived from randomised controlled trial: prospective observational follow-up study.* Bmj, 2011. **342**: p. d3017.

76. Hart, R.G., L.A. Pearce, and M.I. Aguilar, *Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation.* Ann Intern Med, 2007. **146**(12): p. 857-67.

77. Blackshear, J.L. and J.A. Odell, *Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation.* Ann Thorac Surg, 1996. **61**(2): p. 755-9.

78. Boersma, L.V., et al., *Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry.* Eur Heart J, 2016. **37**(31): p. 2465-74.

79. Fuster, V., et al., *ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American*

Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation, 2006. **114**(7): p. e257-354.

80. January, C.T., et al., *2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial FibrillationA Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society*. Journal of the American College of Cardiology, 2014. **64**(21): p. e1-e76.

81. Dunning, J., et al., *Guideline for the surgical treatment of atrial fibrillation*. Eur J Cardiothorac Surg, 2013. **44**(5): p. 777-91.

82. Wyse, D.G., et al., *A comparison of rate control and rhythm control in patients with atrial fibrillation*. N Engl J Med, 2002. **347**(23): p. 1825-33.

83. Roy, D., et al., *Rhythm control versus rate control for atrial fibrillation and heart failure*. N Engl J Med, 2008. **358**(25): p. 2667-77.

84. Chatterjee, S., et al., *Pharmacologic rate versus rhythm-control strategies in atrial fibrillation: an updated comprehensive review and meta-analysis*. Pacing Clin Electrophysiol, 2013. **36**(1): p. 122-33.

85. Pappone, C., et al., *Radiofrequency catheter ablation and antiarrhythmic drug therapy: a prospective, randomized, 4-year follow-up trial: the APAF study*. Circ Arrhythm Electrophysiol, 2011. **4**(6): p. 808-14.

86. Mont, L., et al., *Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study)*. Eur Heart J, 2014. **35**(8): p. 501-7.

87. Walfridsson, H., et al., *Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation: results on health-related quality of life and symptom burden. The MANTRA-PAF trial*. Europace, 2015. **17**(2): p. 215-21.

88. Ludvigsson, J.F., et al., *External review and validation of the Swedish national inpatient register*. BMC Public Health, 2011. **11**: p. 450.

89. Barlow, L., et al., *The completeness of the Swedish Cancer Register: a sample survey for year 1998*. Acta Oncol, 2009. **48**(1): p. 27-33.

90. Ludvigsson, J.F., et al., *The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research*. Eur J Epidemiol, 2009. **24**(11): p. 659-67.

91. Adamsson Eryd, S., et al., *Blood pressure and complications in individuals with type 2 diabetes and no previous cardiovascular disease: national population based cohort study*. BMJ, 2016. **354**: p. i4070.

92. Messerer, M., S.E. Johansson, and A. Wolk, *The validity of questionnaire-based micronutrient intake estimates is increased by including dietary supplement use in Swedish men*. J Nutr, 2004. **134**(7): p. 1800-5.

93. Norman, A., et al., *Validity and reproducibility of self-reported total physical activity--differences by relative weight*. Int J Obes Relat Metab Disord, 2001. **25**(5): p. 682-8.

94. Orsini, N., et al., *Validity of self-reported total physical activity questionnaire among older women*. Eur J Epidemiol, 2008. **23**(10): p. 661-7.

95. Connor Gorber, S., et al., *The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status.* Nicotine Tob Res, 2009. **11**(1): p. 12-24.

96. Kuskowska-Wolk, A., et al., *The predictive validity of body mass index based on self-reported weight and height*. Int J Obes, 1989. **13**(4): p. 441-53.

97. Cox, D.R. and D. Oakes, *Analysis of Survival Data*. 1984, London: Chapman & Hall.

98. Djousse, L., et al., *Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham Study.* Am J Cardiol, 2004. **93**(6): p. 710-3.

99. Frost, L. and P. Vestergaard, *Alcohol and risk of atrial fibrillation or flutter: a cohort study.* Arch Intern Med, 2004. **164**(18): p. 1993-8.

100. Mukamal, K.J., et al., *Alcohol consumption and risk and prognosis of atrial fibrillation among older adults: the Cardiovascular Health Study.* Am Heart J, 2007. **153**(2): p. 260-6.

101. Larsson, S.C., N. Drca, and A. Wolk, *Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis.* J Am Coll Cardiol, 2014. **64**(3): p. 281-9.

102. Andersen, K., et al., *Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study.* Eur Heart J, 2013.

103. Aizer, A., et al., *Relation of vigorous exercise to risk of atrial fibrillation.* Am J Cardiol, 2009. **103**(11): p. 1572-7.

104. Bapat, A., et al., *Relation of Physical Activity and Incident Atrial Fibrillation (from the Multi-Ethnic Study of Atherosclerosis).* Am J Cardiol, 2015. **116**(6): p. 883-8.

105. Azarbal, F., et al., *Obesity, physical activity, and their interaction in incident atrial fibrillation in postmenopausal women.* J Am Heart Assoc, 2014. **3**(4).

106. Everett, B.M., et al., *Physical activity and the risk of incident atrial fibrillation in women.* Circ Cardiovasc Qual Outcomes, 2011. **4**(3): p. 321-7.

107. Thelle, D.S., et al., *Resting heart rate and physical activity as risk factors for lone atrial fibrillation: a prospective study of 309,540 men and women.* Heart, 2013. **99**(23): p. 1755-60.

108. Myrstad, M., et al., *Does endurance exercise cause atrial fibrillation in women?* Int J Cardiol, 2015. **184**: p. 431-2.

109. Wilhelm, M., et al., *Gender differences of atrial and ventricular remodeling and autonomic tone in nonelite athletes.* Am J Cardiol, 2011. **108**(10): p. 1489-95.

110. Myrstad, M., et al., *Effect of years of endurance exercise on risk of atrial fibrillation and atrial flutter.* Am J Cardiol, 2014. **114**(8): p. 1229-33.

111. Mont, L., et al., *Long-lasting sport practice and lone atrial fibrillation.* Eur Heart J, 2002. **23**(6): p. 477-82.

112. Calvo, N., et al., *Emerging risk factors and the dose-response relationship between physical activity and lone atrial fibrillation: a prospective case-control study.* Europace, 2016. **18**(1): p. 57-63.

113. Wong, C.X., et al., *The increasing burden of atrial fibrillation compared with heart failure and myocardial infarction: a 15-year study of all hospitalizations in Australia.* Arch Intern Med, 2012. **172**(9): p. 739-41.

114. Leong, D.P., et al., *Atrial fibrillation is associated with increased mortality: causation or association?* Eur Heart J, 2013. **34**(14): p. 1027-30.

115. Huxley, R.R., et al., *Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study.* Circulation, 2011. **123**(14): p. 1501-8.

116. Egger, M., et al., *Bias in meta-analysis detected by a simple, graphical test.* Bmj, 1997. **315**(7109): p. 629-34.

117. Samitz, G., M. Egger, and M. Zwahlen, *Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies.* Int J Epidemiol, 2011. **40**(5): p. 1382-400.

118. Basavarajaiah, S., et al., *Ethnic differences in left ventricular remodeling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy.* J Am Coll Cardiol, 2008. **51**(23): p. 2256-62.

119. Biffi, A., et al., *Impact of physical deconditioning on ventricular tachyarrhythmias in trained athletes.* J Am Coll Cardiol, 2004. **44**(5): p. 1053-8.

120. Guasch, E., et al., *Atrial fibrillation promotion by endurance exercise: demonstration and mechanistic exploration in an animal model.* J Am Coll Cardiol, 2013. **62**(1): p. 68-77.